NEWER VIRUS DISEASES

Clinical Differentiation of Acute Respiratory Infections



THE MACMILLAN COMPANY
NEW YORK • CHICAGO
DALLAS • ATLANTA • SAN FRANCISCO
LONDON • MANILA
IN CANADA
BRETT-MACMILLAN LTD
GALT, ONTARIO

NEWER VIRUS DISEASES

Clinical Differentiation of Acute Respiratory Infections

JOHN M. ADAMS, M.D., Ph.D.

Professor and Chairman, Department of Pediatrics
School of Medicine, University of California
at Los Angeles

THE MACMILLAN COMPANY
New York

© John M. Adams 1960

All rights reserved—no part of this book may be reproduced in any form without permission in writing from the publisher, except by a reviewer who wishes to quote brief passages in connection with a review written for inclusion in magazine or newspaper.

First printing, February, 1960

Library of Congress catalog card number 59-14044

The Macmillan Company, New York
Brett-Macmillan Ltd., Galt, Ontario

Printed in the United States of America

"I AM AT THIS MOMENT
DEAF IN THE EARS,
HOARSE IN THE THROAT,
RED IN THE NOSE,
GREEN IN THE GILLS,
DAMP IN THE EYES,
TWITCHY IN THE JOINTS,
AND FRACTIOUS IN TEMPER
FROM A MOST INTOLERABLE
AND OPPRESSIVE COLD."

CHARLES DICKENS

From the Presidential Address delivered by John H Dingle before the American Association of Immunologists, Philadelphia, Pennsylvania, April 15, 1958 In *The Collected Letters of Charles Dickens,* Vol 1, p 92, Chapman and Hall, Ltd , London, 1880

FOREWORD

It has been my good fortune to know Dr. John Adams for the past 15 years Being mutually interested, we have had many pleasant and serious discussions and correspondence concerning acute respiratory infections. In spite of the rapid advancement of knowledge concerning these so-called minor diseases, they continue to account for approximately 50 per cent of all cases of total and disabling illness and are the principal cause of absenteeism from play, school, work, and military training. Acute respiratory disease continues to be a major cause of death in infants and children and both primary and contributing cause of death in older age groups

Dr Adams is qualified especially to bring together and correlate the many advances in knowledge of the etiology, pathogenesis, prevention, and management of acute respiratory infections Respiratory and other infections as related to the field of pediatrics have been his major interest for over 20 years. It is important to point out that Dr Adams has included a number of entities (viral, bacterial, and fungal) which are not ordinarily thought to produce or have an acute respiratory phase in pathogenesis As many of the new agents associated with respiratory infections are now known to be viruses for which there is as yet no specific treatment, medical management, particularly in the care of infants and children, becomes important. The chapters on basic concepts, anatomic and physiologic aspects of acute respiratory disease and pneumonia as a basis for medical management are clear and essential.

This volume will be of major interest to all those concerned with the total problem of respiratory disease and its solution Great effort has gone into the preparation of this monograph which fulfills an important need for bringing together current information so essential to the intelligent practice of medicine as it relates to new virus diseases and related entities.

Clayton G. Loosli, M.D., Ph.D.
Dean, University of Southern California School of Medicine, Los Angeles

PREFACE

Recent outstanding contributions to our fundamental knowledge of acute respiratory tract infections, especially those caused by *newly discovered viruses*, have been numerous. Accordingly, the practicing physician, who is called upon daily to treat these ubiquitous diseases of man, should no longer be content with diagnoses such as "tonsillitis," "the flu," or "the virus that is going around." The intelligent management of his patient's illness is dependent upon accurate diagnosis. To this end the following chapters are designed to inform the reader of the epidemiologic and clinical features of the various influenza-like diseases, with emphasis on etiologic diagnosis, rather than anatomic, as a basis for wise therapy.

In modern clinical medicine there are an increasing number of diagnostic tests for virus and rickettsial diseases. However, in spite of these new procedures, the practicing physician must become well acquainted with the clinical features of these diseases as entities with a specific etiology. Epidemiology, pathogenesis, and clinical symptoms and signs of disease are the most essential features for an initial working diagnosis. Confirmation of the initial impressions in many instances will have to come from the laboratory

Influenza, the prototype respiratory disease of viral origin, is dealt with in considerable detail Emphasized are its epidemic features, the various types and strains, the potential for secondary bacterial complications, the pathology of the uncomplicated disease, the high mortality in infancy and old

age, and the possible relationship to sudden unexpected deaths in the early months of life. Also discussed are the new *myxoviruses*, the para-influenza viruses (hemadsorption and croup-associated), as well as other respiratory viruses and the diseases which they cause.

The new *adenovirus* infections are presented in detail, with emphasis on the clinical diagnosis of the various types of infection, their prevention, and their relationship to the general problem of common respiratory disease.

A separate chapter is devoted to diseases caused by the newly named *enteroviruses*, which include the two large groups of Coxsackie viruses (A and B), the *polioviruses*, and the recently discovered ECHO (Enteric Cytopathogenic Human Orphan) viruses. Although these groups of viruses are renowned for their etiologic role in many of the aseptic meningitides, the practitioner must be aware that in each of these groups, including the *polioviruses*, there are distinct symptoms and signs of respiratory tract infection, and these may be the sole clinical manifestations of illness

Several chapters deal with entities such as infectious mononucleosis, Q fever, and psittacosis, wherein respiratory symptoms and signs are often the predominant feature Scarlet fever, diphtheria, and pertussis are discussed in a chapter devoted to bacterial infections of the respiratory passages, and emphasis is given to group A *beta hemolytic streptococcus* as the major cause of primary pharyngitis due to bacteria

A review of the pneumonias encompasses recent knowledge of giant cell pneumonia, plasma cell pneumonia, and atypical pneumonia The latter undoubtedly represents part of the spectrum of most of the diseases discussed in this book A section is included on pneumonia as a cause of sudden unexpected death in infants

The respiratory aspects of certain fungal infections, such as coccidioidomycosis and histoplasmosis, are included There is

also a brief discussion of primary tuberculosis, which, in its milder manifestations, might well be considered a mild, moderate, or severe "cold."

A chapter has been devoted to the common cold as a possible entity, even though we recognize that every disease under discussion in this book at some time in its development may mimic the symptoms and signs of what people (patients and doctors) call "colds" Also included is a brief discussion of allergic rhinitis and its relationship to the common cold.

The author wishes to extend his appreciation to Clayton Loosli for critically reviewing the manuscript and writing the Foreword to this book David Imagawa, an esteemed friend and colleague, has contributed immeasurably over the years to the studies which have made this volume a reality.

J M A.

CONTENTS

Chapter One

INTRODUCTION AND BASIC CONCEPTS

INTRODUCTION

Respiratory diseases are the commonest illnesses of man, and as such account for a major responsibility of all practicing physicians Although there is still a great deal to be learned about common respiratory tract infections, in the past 5 to 10 years alone, several new groups of virus diseases have been delineated Many of the newly discovered viruses are known to be etiologically responsible for common respiratory diseases Several surveys now indicate clearly that respiratory infections constitute the commonest cause of illness in man and the bacterial, fungal, and viral agents known to cause these diseases still account for a relatively small percentage of them Dingle and Feller (1956) found 66 per cent of all illnesses are respiratory and about 95 per cent of these are unknown etiologically Their data from ten years of intensive study of families in Cleveland indicate that approximately 40 per cent of all illnesses can be classified as common colds on clinical grounds. Evans (1958), in a study of 710 university students sick enough to be admitted to the infirmary with acute respiratory illnesses, stated that approximately 10

per cent were due to bacteria and 10 per cent were due to viruses, leaving 80 per cent with unknown conditions. The great majority of the bacterial causes were attributed to streptococci, and influenza accounted for most of the viral illnesses identified in his study.

The sulfonamide drugs and antibiotics have markedly reduced many of the tragic consequences of acute respiratory disease such as secondary pneumonia, otitis media, and mastoiditis; however, the primary illnesses still remain virtually untouched in incidence and severity. Many might still question the over-all significance of the common respiratory diseases, and when compared with the pestilences and infections which swept away our ancestors, such as smallpox, typhus, and yellow fever, they do seem insignificant However, their importance cannot always be measured directly since we are more aware than ever of their basic role as precursors of serious disease. The significance of primary respiratory infection in the pathogenesis of diseases such as bacterial meningitis, acute epiglottitis, and pneumonias of various types is yet to be determined fully. We are, however, familiar with the fact that "of the legion of bacterial species in man's external and internal environment, only comparatively few ever cause disease" (Andrewes, 1958) This did not at first appear to be the case with viruses which must multiply within cells Research has been directed at pathogenesis and cause of disease, and when a virus was found, an etiologic relationship was frequently considered to be associated.

Recent research employing tissue culture methods has revealed many new viruses, but a direct association with disease is not always possible Awareness of these facts is essential for the proper evaluation of the patient's illness Latent viruses may be responsible for inapparent disease or no disease at all The baby who is brought to the physician from a family which has recently experienced a common respiratory disease may

be suffering or dying from acute *Hemophilus influenzae* (bacillus), a type B meningitis. Is the illness unrelated to the current family epidemic? In the present state of our knowledge we must conclude that the family epidemic of acute respiratory disease probably played a most significant pathogenic role in the infant's illness. Such a mortality is rarely attributed to the primary illness, yet its significance cannot be overlooked as a basic factor in the infant's serious disease or demise.

Because the practitioner is called upon daily to diagnose and treat common acute respiratory diseases, it is imperative that he equip himself to do a better job The widespread and almost indiscriminate use of drugs (antibiotics, in particular) for most of these infections is not indicated Although, as yet, we do not have a quick and easy way to make an accurate diagnosis of most of the common respiratory tract infections, we do have knowledge that the majority of these illnesses are not primarily due to bacteria for which antibiotics are readily available. When complications are evident or even highly suspected, wise choice of an antibiotic can usually be made.

The problem, therefore, is not a simple one which can be resolved with a diagnosis of "tonsillitis" or "nasopharyngitis," probably due to a "virus." Rather, an etiologic approach to the diagnosis should be made on the basis of a good history and physical examination backed up by laboratory tests and a thorough knowledge of the various possibilities These are, indeed, many and complex and require a knowledge of epidemiology, etiology, and pathogenesis of common respiratory diseases No criticism is intended but rather a plea for a serious and more scientific approach to these common everyday problems

Brief examples of the clinical approach to an etiologic diagnosis might be cited Influenza is an epidemic virus disease occurring in the winter months as a rule It is characterized by clinical features such as sudden onset of fever, sore throat,

myalgia, and acute pharyngitis without exudate. A diagnosis of "the flu" outside of an epidemic is almost bound to be incorrect, whereas during an epidemic, such a diagnosis of any acute respiratory illness has about an 80 per cent chance of being correct. Many city, county, and state laboratories are now equipped to confirm the diagnosis. Coxsackie A infections usually occur in the summer months, and many of these may be distinguished by vesicular lesions in the pharyngeal areas. Adenovirus infections may also occur in epidemics and have been described as causing typical pharyngoconjunctival fever. Common exudative or follicular tonsillitis may be due to one of the adenoviruses. The majority of these illnesses are not "strep throats," but may occasionally become complicated by a streptococcal infection. However, when the characteristics of streptococcal disease are evident, such as dirty gray confluent membranes on the tonsils with high fever and leukocytosis, a nose and throat culture followed by penicillin is definitely indicated. These sketchy descriptions are only samples of the clinical approach to the problem All of these conditions are presented in detail in the following chapters in which further diagnostic and clinical pathologic features are outlined

BASIC CONCEPTS

Clinical Spectrum

It is most essential that an appreciation of the clinical spectrum of diseases of the respiratory passages be made an intimate part of our thinking. It is definitely known that the influenza viruses, the adenoviruses, the polioviruses, and others may infect man and cause no symptoms whatsoever They may produce a mild illness which is commonly referred to as "a cold" or "the flu" or more serious disease, when such diagnoses as "bronchitis" or a "touch of pneumonia" may be made In certain highly susceptible individuals, any of the etiologic

agents mentioned previously may produce serious disease or death. Primary tuberculosis was probably one of the first respiratory diseases to alert the physician to the importance of the clinical spectrum It is well recognized that most initial tuberculous infections are mild or inapparent and may be discovered months or years later as a result of a positive tuberculin skin test The more severe forms of tuberculosis are often the result of advancing infection such as adenitis, pleurisy, miliary, or meningeal disease. These will serve to emphasize the spectrum of illness which is also determined by many factors such as age, race, infecting dose, and general hygiene.

In Figure 1, a graphic representation of the spectrum of disease is depicted. The wavy section running horizontally across the lower part of the graph represents what might be called a reticular zone, or area of awareness, *above* which we can recognize illness, *below* or in which we cannot by ordinary clinical means The course of disease is visualized as beginning below the area of awareness, such as "incubation period," and traversing along the developmental line to rise above the surface and manifest itself as mild, moderate, or severe illness, ending in death if recovery or a remission does not occur The course of disease may terminate with complete recovery below

SPECTRUM OF DISEASE

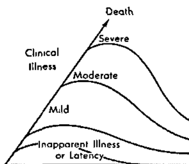


Figure 1. Graph illustrates the clinical spectrum of disease The developmental line traverses from the area of inapparent infection into the clinical area where disease may be manifest by mild, moderate, or severe signs and symptoms The developmental lines lead either to recovery or on to death

myalgia, and acute pharyngitis without exudate. A diagnosis of "the flu" outside of an epidemic is almost bound to be incorrect, whereas during an epidemic, such a diagnosis of any acute respiratory illness has about an 80 per cent chance of being correct. Many city, county, and state laboratories are now equipped to confirm the diagnosis. Coxsackie A infections usually occur in the summer months, and many of these may be distinguished by vesicular lesions in the pharyngeal areas. Adenovirus infections may also occur in epidemics and have been described as causing typical pharyngoconjunctival fever. Common exudative or follicular tonsillitis may be due to one of the adenoviruses. The majority of these illnesses are not "strep throats," but may occasionally become complicated by a streptococcal infection. However, when the characteristics of streptococcal disease are evident, such as dirty gray confluent membranes on the tonsils with high fever and leukocytosis, a nose and throat culture followed by penicillin is definitely indicated. These sketchy descriptions are only samples of the clinical approach to the problem. All of these conditions are presented in detail in the following chapters in which further diagnostic and clinical pathologic features are outlined.

BASIC CONCEPTS

Clinical Spectrum

It is most essential that an appreciation of the clinical spectrum of diseases of the respiratory passages be made an intimate part of our thinking It is definitely known that the influenza viruses, the adenoviruses, the polioviruses, and others may infect man and cause no symptoms whatsoever They may produce a mild illness which is commonly referred to as "a cold" or "the flu" or more serious disease, when such diagnoses as "bronchitis" or a "touch of pneumonia" may be made In certain highly susceptible individuals, any of the etiologic

agents mentioned previously may produce serious disease or death. Primary tuberculosis was probably one of the first respiratory diseases to alert the physician to the importance of the clinical spectrum It is well recognized that most initial tuberculous infections are mild or inapparent and may be discovered months or years later as a result of a positive tuberculin skin test. The more severe forms of tuberculosis are often the result of advancing infection such as adenitis, pleurisy, miliary, or meningeal disease. These will serve to emphasize the spectrum of illness which is also determined by many factors such as age, race, infecting dose, and general hygiene.

In Figure 1, a graphic representation of the spectrum of disease is depicted The wavy section running horizontally across the lower part of the graph represents what might be called a reticular zone, or area of awareness, *above* which we can recognize illness, *below* or in which we cannot by ordinary clinical means. The course of disease is visualized as beginning below the area of awareness, such as "incubation period," and traversing along the developmental line to rise above the surface and manifest itself as mild, moderate, or severe illness, ending in death if recovery or a remission does not occur The course of disease may terminate with complete recovery below

SPECTRUM OF DISEASE

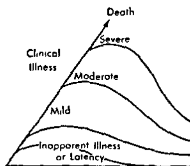


Figure 1. Graph illustrates the clinical spectrum of disease The developmental line traverses from the area of inapparent infection into the clinical area where disease may be manifest by mild, moderate, or severe signs and symptoms The developmental lines lead either to recovery or on to death

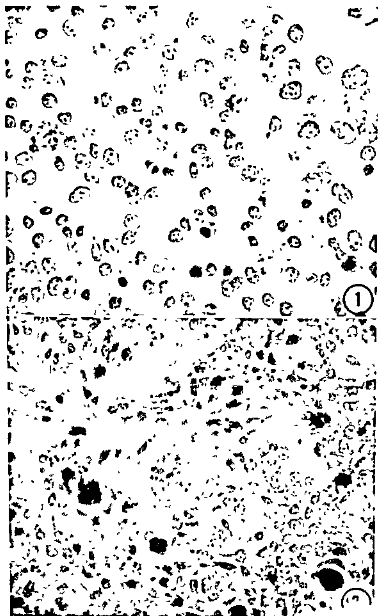
the level of clinical awareness or a "latent infection" may persist. Andrewes (1958) defines these infections as "inapparent infections which are chronic with some measure of equilibrium established between host and parasite." Such a situation might be represented by a positive tuberculin developing in a patient without clinical signs of illness, but a latent infection persists which may some day become active, at which time the course of disease would cross into the area of awareness and proceed to a clinical illness of varying degree.

It is not improbable to consider that other diseases proceed in a similar fashion, manifesting various phases of the spectrum of disease. Sufficient evidence is available to indicate that influenza may be inapparent, mild, or severe and rarely leads to death Latency is not readily apparent in this disease although a carrier state has been reported. Poliomyelitis would appear to offer another example of a well-established disease with a broad clinical spectrum, the major portion of which may actually reside in the subclinical area

Virus Research

Andrewes (1954–55) points out the great strides which *have been made in virology by the development of new meth*ods of investigation such as the use of suckling mice, by which tool Dalldorf and associates (1949) discovered whole new groups of viral agents now known as Coxsackie viruses These viruses are vitally important in diseases of man, and tremendous strides in our understanding of these diseases have been made by many investigators since their discovery 10 *years ago. We now recognize that they not only produce var-*

Figure 2. Two photomicrographs are shown to illustrate (1) normal tissue culture cells as they appear when stained, and (2) cytopathogenesis, which occurs when the culture is infected with viruses The cells are HeLa cells, and the cytopathology is produced by the measles virus The stain is hematoxylin and eosin



ious forms of acute respiratory and enteric disease but they may also cause meningitis and myocarditis. The suckling mouse has made possible highly significant research into the etiology of mouse leukemia which would appear to be viral in origin (Gross, 1950). Outstanding advances were made by the adaption of tissue culture methods to practical viral research when Enders, Weller, and Robbins (1949) cultivated the poliomyelitis virus in tissues other than those of the nervous system. In addition, they showed that the destructive effects in culture tubes could be used to quantitate viruses and antibodies, and thus the development of effective vaccines was made possible.

In Figure 3, *unstained* photomicrographs illustrate the appearance of normal tissue culture and cytopathogenesis as it is seen in culture tubes which are followed daily in the laboratory.

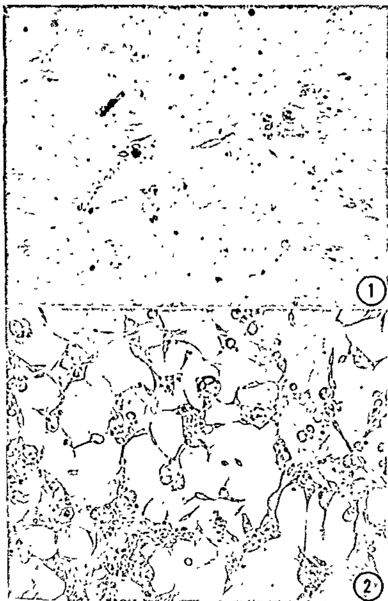
The discovery of the *adenoviruses* by Rowe, Huebner, Gilmore, Parrott, and Ward (1953) in tonsils and adenoids removed at operation was the direct result of new tissue culture methods At the same time Hilleman and Werner (1954) discovered that these identical viruses were etiologically responsible for acute respiratory disease in human beings These advances, including the production of successful *adenovirus* vaccines, are discussed in detail in Chapter Three.

Latency

The concept of latency in virus diseases is becoming recognized increasingly and has real significance for the clinician Many viruses are being isolated by numerous laboratories

---

Figure 3. Two photomicrographs of tissue culture cells as they appear in the test tube *unstained* The upper picture (1) shows normal cells, and



1
2

equipped to do virology, and consequently an evaluation of such isolations by the clinician will be necessary. Many of the *adenoviruses* were isolated from adenoid and tonsil tissues removed from essentially well children, and the isolation rates have been much higher than the incidence of acute disease due to those agents among such children. Evans (1958) studied third-grade school children for the prevalence of *adenovirus* infection and concluded that less than 1 child in 100 contracted clinical illness associated with an *adenovirus* during a particular respiratory season. He also found a rate of about 1 per cent among university students studied over a four-year period. The high incidence among military recruits is difficult to understand unless it can be explained by intimate association in military camps.

Latency implies that the parasite and host have learned to exist together and many viral infections are known to exist unobserved in their natural host. In the instance of herpes simplex infections certain events, such as fever, menstruation, excessive sunshine, or trauma to the lips, may activate an inapparent or latent infection, and lesions will then appear in the mouth and on the lips or skin areas which have been exposed or injured.

In the experimental laboratory, latency in animal viruses may be revealed by the simple procedure of passage of organ suspensions such as brain or lung from one animal to another Viral infections seem to appear spontaneously but undoubtedly represent the phenomenon of latency in which the quiet relationship established by the parasite and host is upset This fact has placed some real limitations on the use of mice in particular for isolation studies

The fact that many different types of *enteroviruses* have now been isolated from the stools of apparently well individuals may represent another example of latency to which the

clinician must be alert. A new problem arises with viruses which is similar in many ways to the old problem with bacteria, that of deciding whether or not the isolated agent is responsible for the patient's illness. The fact remains that many bacterial and viral agents revealed by various culture methods may *not* be involved directly in the patient's illness. Special antibody tests comparing early and late serum samples are usually necessary for a more definitive answer. Unfortunately these are often impractical or unobtainable, and the true diagnosis may remain unproved. Therefore, the clinician must constantly be on guard and extremely cautious in his interpretation of what may appear at first glance to be an obvious explanation for his patient's illness. The primary illness represents the greatest challenge, whereas the secondary complication may dominate the clinical picture and a diagnosis is readily explained on the basis of the findings caused by the secondary invader

Age Factors

It is particularly important that we recognize age differences, which are frequently related to the severity of disease, especially when seen in a family epidemic Many infections occur much more severely in prematurely born babies or infants than in older children or adults. We are also aware that certain so-called childhood diseases such as chickenpox, measles, and poliomyelitis may manifest themselves in very severe form in adult patients We know little of the basic factors underlying these differences, which we can only recognize as being related to age. Experimentally, newborn mice are found to be highly susceptible to certain types of infections such as those due to Coxsackie viruses, whereas older animals are found to be resistant In the case of *polioviruses* newborn mice are less susceptible than older animals

Secondary Infection

It is important clinically to recognize what is *primary* and what is *secondary* in respiratory tract infections. The occurrence of mixed infections cannot be overemphasized, and the actual symptomatology which the patient exhibits may be more related to the secondary complicating organisms than to the primary agent. Complications may occur in concert with or follow very closely behind the primary illness. This fact has led to a great deal of confusion for many years. Epidemics may vary from community to community or within families in a community, as a result of varying secondary complicating organisms Man is now recognized as a common carrier of many bacteria, and we are gradually becoming aware of the importance of fungal as well as viral agents which apparently have established a symbiotic relationship between the host and parasite.

It is conceivable that almost any sequence of events might occur to initiate clinical disease. However, most recent studies reveal that the majority of primary respiratory tract infections are probably due to viruses. These are considered to be airborne and highly contagious for the susceptible individual, this is most obvious at times of influenza and measles epidemics In the case of certain of the new *adenovirus* infections, highly epidemic characteristics have been manifested in new recruits in the military population Conceivably epidemics could occur in institutions such as schools and industry In the now-classic study of illnesses in families which is going on in Cleveland under the direction of John H Dingle, the etiologic agents responsible for most of the common respiratory diseases are considered to be nonbacterial. The measles virus and various types of influenza viruses have been recognized for many years as the cause of primary respiratory

tract infections which may commonly be complicated by various bacterial organisms.

Pathogenesis

The pathogenesis of acute respiratory disease is not completely understood, but it would seem illogical to continue to refer to upper and lower respiratory tract infections A dividing line would be difficult to determine in most patients, and a thorough clinical appraisal often reveals that even mild infections are not confined to the upper respiratory passages Cough, a common symptom of mild respiratory tract disease, usually indicates some irritation in the middle or lower respiratory passages. Experimental studies have clearly established the fact that the basic mechanism in the development of pneumonia is aspiration (Robertson, 1943). Infectious material from the upper respiratory tract may be aspirated and thus produce disease lower down in the pulmonary tree The lung, which is an internal organ, is constantly exposed to outside air. Sticky mucus in the respiratory passages undoubtedly catches many organisms which the cilia in turn move out of the pulmonary tree The conjunctiva may be considered a common portal of entry, and tears are known to have a high lysozyme content, which is bacteriostatic. They likewise serve to rid the conjunctiva of many of the organisms that come in contact with it. The epiglottis is an important defense organ, but incomplete in its function during chilling or anesthesia Mucous secretions in the lower respiratory passages combine with cough and cilia as essential mechanisms for eliminating foreign material Phagocytosis and lymphatic drainage in the lower parts of the pulmonary tree are significant mechanisms of defense The lungs which are normally sterile are undoubtedly kept so by the various mechanisms that have just been referred to

Many factors underlie the development of respiratory tract infections, and probably one of the most important is the degree of specific immunity. It might be further defined as varying susceptibility of the host. Factors which make up the host defenses are influenced by environmental stressing situations such as fatigue, chilling, psychogenic disturbances, and obvious exposure to disease. A combination of agents, therefore, as well as host factors, plays an important role in the pathogenesis or development of respiratory tract infections

Evidence indicates that congestion and irritation resulting from infections in the respiratory passages may interfere with elimination, and thus favor the development of secondary infections. Following obstruction and congestion as well as local irritation produced by primary respiratory disease, secondary involvement in the form of bacterial infection of the sinuses, inner ears, lymphatics and their glands, and the lower pulmonary passages occurs. *The escape of bacterial-laden fluids past the epiglottic barrier plays a much more important role in the inception of pulmonary disease than does the inhalation of infective droplets. In primary epidemic respiratory disease*, air-borne infection is recognized in influenza (Loosli, Robertson, and Puck, 1943), and would appear to be the outstanding factor *in* the spread of measles and many other respiratory virus diseases A lateral body-section roentgenogram of an infant is shown in Figure 4, to illustrate the angle of drainage that obtains when the patient is placed in the prone position This position is advocated in order to minimize the dangers of aspiration, to prevent pneumonia, and to treat cough related to drainage in the postpharyngeal area

The clinician is faced with the problem of treatment and prevention and is constantly intrigued by the idea that antibiotics may be the answer to the problem However, the use of antibiotics and chemotherapeutic agents *in the treatment* of measles has been shown by Weinstein (1955) not to reduce

the incidence of secondary complications, but they may even be increased as a result of the emergence of certain antibiotic-resistant organisms. Organisms such as the influenza bacillus

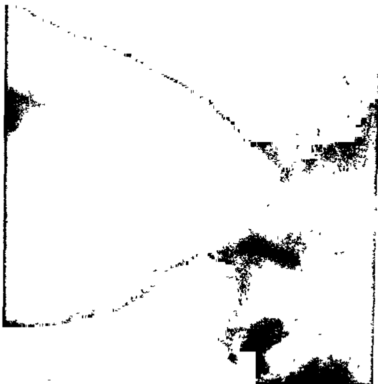


Figure 4. A body-section roentgenogram of an infant in the prone position illustrating the slope of the main respiratory passages. This position is advocated to prevent aspiration, to promote drainage, and to ameliorate cough due to obstruction caused by the accumulation of exudate

have been the primary complicating organisms rather than the streptococcus and pneumococcus so commonly recognized prior to the days of specific therapy. Certainly a critical ap-

praisal of the routine prophylactic use of antibiotics in common respiratory disease is necessary, and at the present time the writer does not favor their routine use in the majority of these infections, unless indications are apparent, at which time a wise choice of therapeutic agents should be made.

Virus Interference Phenomenon

The phenomenon of virus interference may have important implications for the clinician. In general the phenomenon of interference is manifested when a virus capable of causing illness or death fails to do so when inoculated along with or following a second virus which by itself fails to produce symptoms. An example of interference cited by Burnet and Lind (1954) *occurs when two influenza strains are inoculated into* mouse brain. One virus which is capable of producing death in a very high dilution will fail to do so except at very concentrated strength, and weaker concentrations of what might be an otherwise fatal infection may be prevented entirely by the presence of a nonpathogenic virus. Vilches and Hirst (1947) showed that nonneurotropic influenza viruses would also protect against one strain of a completely unrelated virus, that causing western equine encephalitis. It is indeed remarkable, according to Burnet (1955), how readily the multiplication of a highly adapted strain of western equine encephalitis virus can be inhibited in the mouse brain by the prior injection of such unrelated pathogens as influenza viruses

The growth of influenza viruses in the allantoic cavity of the chick embryo provides an excellent situation for the study of interference It a large dose of undiluted virus is inactivated by ultraviolet irradiation and injected into the allantoic cavity subsequent inoculation of a small dose of active virus of any type will produce no demonstrable evidence of infection Killed virus, heated to 56 C for 30 minutes, is equally effective as an interfering agent The implications for the physician

are complex indeed, and although double infection in an animal is recognized, clinically it is rare to see a patient who is suffering from one virus disease become acutely involved by another. This would seem like a logical or opportune time to attack, but the phenomenon of virus interference may be a most significant mechanism of nature to minimize or prevent double, triple, or more infections.

Burnet (1955) points out that it is of no great interest if a second virus cannot multiply in a cell that has suffered lethal damage from the first. It is, however, important when the interfering virus enters and initiates the process of multiplication in the cell, fails to damage it, and yet after an appropriate period renders it insusceptible to action of the second challenging virus Burnet (1955) emphasizes that this may well be the central problem of virology:

> What determines why a virus "potentially" capable of initiating a process of multiplication that can go on to complete necrosis of the cell will, under some circumstances, produce no overt pathological changes whatever? It seems only reasonable to believe that this failure to continue the initiated process is a type of auto-interference and that its interpretation would almost automatically provide an interpretation of interference in general

The clinician and epidemiologist are tempted to ask the virologist what the possible relationship of the interference phenomenon might be to the changing pattern of epidemiology The appearance of several forms of aseptic meningitis, assuming epidemic proportions at a time when poliomyelitis is normally the predominant illness, is of extreme interest and importance to the clinician Have we failed to diagnose these diseases in the past, or merely referred to them as nonparalytic poliomyelitis, or were they formerly interfered with in some manner and now are freer to produce recognizable epidemic disease?

Diagnosis (Basic Considerations)

A further basic concept that deserves more emphasis is the vital importance to the clinician and student of medicine of an accurate diagnosis based primarily on etiology. Vague anatomic terms, such as tonsillitis and bronchitis, provide little help toward an intelligent approach to treatment and prognosis. *It is now clear that literally dozens of different agents* may cause acute tonsillitis, all the way from rare causes such as *Pasteurella (bacterium) tularensis*, reported by Hughes and Etteldorf (1957) as the cause of oropharyngeal tularemia, to *beta hemolytic streptococcus* and possibly other bacteria, and thence to the almost innumerable viral agents now recognized as primary etiologic factors in common respiratory diseases.

Certain basic laboratory approaches exist for diagnosis and can be listed as: (1) examination of infected tissues for pathologic alterations, (2) isolation and identification of the infecting agent, (3) determination of rises in antibody titer during the course of illness which indicate the presence of specific disease, and (4) detection of viral antigens in lesions, such as is now being accomplished by means of fluorescein-labeled antibodies in clinical specimens. The nature of the disease may determine largely which method of diagnosis is best *suited to the particular patient Microscopic methods are of* limited value but may be employed in the case of vaccinia or other viral infections, in the examination of spinal fluid and urinary sediment as well as pharyngeal smears. Confirmation is often necessary serologically or through the isolation of the causative agent These procedures are time consuming and are usually not as available or practical as serologic methods *Serologic tests as a rule find far greater* usefulness than either the microscopic or isolation approach Serologic methods are of little use when the etiology is unknown, in which case isolation methods would be more valuable Inasmuch as an eti-

ologic diagnosis of these common respiratory tract infections is highly advocated, as opposed to anatomic terms, it is necessary that laboratory methods be employed in addition to increased clinical knowledge of these diseases.

A paramount consideration in the diagnostic evaluation of a patient with a possible viral infection is the fact that the same clinical syndrome may be caused by many different agents Aseptic meningitis, for example, is caused by *polioviruses*, mumps, herpes, and lymphocytic choriomeningitis viruses, many different types of leptospira, and certain Coxsackie and ECHO viruses. Likewise influenza-like illnesses may be produced by three different types of influenza, various other *myxoviruses*, psittacosis, Rift Valley fever, dengue fever, *adenoviruses*, and infectious mononucleosis

An additional complicating factor in etiologic diagnosis is the relative ease with which viruses may be isolated As pointed out previously, mere isolation does not always establish the agent as the causal factor in the patient's illness Viruses persist in human hosts for long periods of time, and the isolation of such agents as herpes, *polioviruses*, and ECHO and Coxsackie viruses does not necessarily indicate that the virus is responsible for the patient's illness A consistent clinical and epidemiologic pattern is essential in establishing the relationship of the isolated agent to the disease Different viruses, having the same seasonal and geographic occurrence as poliomyelitis and encephalitis viruses, may cause inapparent as well as clinical disease In one season, one patient may have inapparent infection with one virus and clinical infection with another Aseptic meningitis may be caused by either agent, and only by antibody studies with both agents can one establish a true diagnosis Further diagnostic difficulties are encountered when rare dual infections occur, as may happen with *polioviruses*, Coxsackie or ECHO viruses Inasmuch as two viruses have been isolated from the same stool samples of

paralytic patients and antibody rises to two agents have been demonstrated, the *poliovirus* is usually held responsible although the possible role of Coxsackie and ECHO viruses may be in some way related. *Serologic studies are therefore necessary* when multiple viruses are isolated. The Coxsackie and ECHO viruses were originally isolated in poliomyelitis stool surveys, and their interrelationships have not as yet been fully worked out.

The complement fixation test is the mainstay of the virus diagnostic laboratory, largely because it is relatively simple and economical. *These tests are available for a large number* of viral diseases: influenza A and B, Newcastle disease, herpes simplex, Colorado tick fever and other *arborviruses*, the entire adenovirus group, and poliomyelitis. It is most significant when a fourfold or greater rise in titer occurs. The principle of the complement fixation test is based on the presence of a thermolabile substance which is removed or inactivated by heating and then a known amount of complement may be added in the form of fresh guinea pig serum. Virus plus complement is added to serial dilutions of the serum to be tested. An indicator system consists of a mixture of sheep erythrocytes and antibody to sheep cells which is known as hemolysin The *occurrence or nonoccurrence of hemolysis indicates whether* antibody to the virus or antigen used in the test is present in the serum

Collection of Specimens and Laboratory Procedures

In order to facilitate *the isolation of viruses, the proper collection* of appropriate materials is essential The inoculation of susceptible animals, egg embryos, or suitable tissue cultures depends in large part on the agents *that are being looked for* In the laboratory the inoculum is prepared by filtration or differential centrifugation, or by the use of *bactericidal drugs in* order to eliminate bacteria. The earlier in the illness specimens

are obtained the more chance there is of an isolation. Most viruses may be preserved by freezing, and collections at the bedside are often placed immediately in wide-mouthed Thermos jars containing pieces of solid carbon dioxide or dry ice, in which state the virus may be preserved for travel and for long periods of time prior to inoculation. Temperatures of between −20° and −70° C should be employed from the time of collection until inoculation.

The main laboratory animals used in virus isolation include mice, hamsters, cotton rats, guinea pigs, rabbits, and monkeys. Occasionally, one- to two-day-old mice are employed, particularly when Coxsackie viruses are being looked for. Tissue culture methods are available in many laboratories, and cells may be maintained in simple test tube cultures, 1 to 2 ml of nutrient fluid containing balanced salt solutions and various growth factors are employed to provide nourishment to the cells Cells may then be examined under the microscope through the glass wall of the test tube each day with the low-power objective The cytopathogenic effect referred to previously (Figs 2 and 3) occurs when virus begins to destroy tissue This effect can be inhibited by specific immune serum and provides an excellent neutralization test It also makes possible typing of *polioviruses* and quantitating the amount of antibody. In addition to animal and tissue cultures, chick embryos are used particularly for the isolation of influenza viruses Further discussion of diagnostic procedures is presented in specific chapters that follow

Classification of Acute Respiratory Diseases

It would be difficult, if not impossible, to attempt to classify the widely varied and complex causes of respiratory disease, and therefore an attempt will be made only to group these diseases and etiologic agents into fairly large categories to provide a sort of working differential diagnosis. The chapters

of this book, beginning with the influenzas, would serve as a basic outline, but a tabular presentation with a few more details, including the etiologic agent when known, is shown in the accompanying Table 1.

Table 1

ACUTE RESPIRATORY DISEASES

DISEASE	ETIOLOGY:
Epidemic influenza	*Myxoviruses* Influenzae A, B, and C
Para-influenza 1, 2, and 3 (infantile croup)	Para-influenzae 1, 2, and 3 (hemadsorption viruses) (croup-associated [CA] virus)
Adenovirus infections	*Adenoviruses* Types 1–24
Acute respiratory disease (ARD)	*Adenoviruses,* types 4 and 7, also 3 and 14
Keratoconjunctivitis	*Adenoviruses,* type 8, also 3 and 7a
Acute follicular conjunctivitis	*Adenoviruses,* types 3, 6, 7a, 9, and 10
Pharyngoconjunctival fever	*Adenoviruses,* types 3, 7a, 14, also 1, 2, 5, and 6
Exudative tonsillitis and or pharyngitis	*Adenoviruses* types 1, 2, 3, and 5
Virus pneumonia in infants and adults	*Adenoviruses* types 7a, 4, and 7, also 1 and 3
Enteric virus diseases	*Enteroviruses* Coxsackie A and B viruses *Polioviruses* types 1, 2, and 3 ECHO viruses types 1–25 (*HE virus*)
Vesicular pharyngitis	Coxsackie A viruses
Acute pharyngitis	Coxsackie A and B viruses
Poliomyelitis	*Polioviruses,* types 1, 2, and 3

Table 1 (Continued)

ACUTE RESPIRATORY DISEASES

DISEASE:	ETIOLOGY:
Respiratory illness in infants	ECHO virus, type 20 (JV-1)
Respiratory-enteric disease	*Reoviruses*, types 1, 2, and 3
Measles (rubeola)	Rubeola virus
German measles (rubella)	Rubella virus
Psittacosis	Psittacosis-ornithosis group of viruses
Q fever	Rickettsia *Coxiella burnetii*
Leptospirosis	Spirochete *Leptospira icterohaemorrhagiae*
	L. canicola
	L pomona and 4 other types
Tuberculosis	Bacteria *Mycobacterium tuberculosis*
	M bovis
Scarlet fever and streptococcal pharyngitis	Group A *beta hemolytic streptococcus*
Diphtheria	*Corynebacterium diphtheriae*
Pertussis	*Bordetella pertussis* and *parapertussis*
Coccidioidomycosis	Fungus *Coccidioides immitis*
Histoplasmosis	*Histoplasma capsulatum*
Moniliasis	*Candida albicans*
OTHER RESPIRATORY DISEASES	
Lymphocytic choriomeningitis	L C M virus
Infectious mononucleosis	Undetermined
Acute infectious lymphocytosis	Undetermined
Respiratory tract infections	J H and 2060 viruses, respiratory syncytial virus (RS), the Coe virus, and "U" or Uppsala virus
Primary atypical pneumonia	PAP virus

REFERENCES

Andrewes, C. H. (1954–55): The new look in virus research, Lectures on the Scientific Basis of Medicine, 4 18.

Andrewes, C. H (1958)· Viruses in health and disease, *Perspectives in Biology and Medicine*, 1.211.

Burnet, F. M (1955): *Principles of Animal Virology*. Academic Press, New York.

Burnet, F. M , and Lind, P E. (1954). Reactivation of heat-inactivated influenza virus by recombination, *Australian J Exper. Biol. & M Sc.*, 32.133.

Cramblett, H G.; Kasel, J. A , and Utz, J. P. (1959). Respiratory illness in children simultaneously infected with hemadsorption virus type 1 and a newly recognized HeLa enterovirus (HE), *Pediatrics*, 24:234

Dalldorf, G , Sickes, G M , Plager, H , and Gifford, R. (1949). Virus recovered from feces of "poliomyelitis" patients pathogenic for suckling mice, *J Exper Med*, 89 567

Dingle, J H , *et al* (1949) Study of respiratory infections in families, *Tr A. Am Physicians*, 62 99

Dingle, J H , and Feller, A E (1956) Noninfluenzal viral infections of the respiratory tract, *New England J Med*, 254 465

Enders, J F , Weller, T H , and Robbins, F C (1949) Cultivation of Lansing strain of poliomyelitis virus in cultures of various human embryonic tissues, *Science*, 109.85

Evans, A. S (1958)· Adenovirus infections in children and young adults with comments on vaccination, *New England J. Med*, 259 464

Gross, L (1950) Susceptibility of · ' fant and resistance of adult mice of C3H and C5 inoculation of AK

Hilleman, M. R., and Werner, J. H. (1954): Recovery of new agent from patients with acute respiratory illness, *Proc. Soc. Exper. Biol & Med.*, **85**:183

Hughes, W. T., and Etteldorf, J. N (1957): Oropharyngeal tularemia, *J. Pediat*, **51**,363

Loosli, C. G; Robertson, O H; and Puck, T. T. (1943): The production of experimental influenza in mice by inhalation of atmospheres containing influenza virus dispersed as fine droplets, *J. Infect Dis*, **72**.142

Robertson, O H (1943). Newer knowledge concerning inception of pneumonia and its bearing on prevention, *Ann. Int. Med*, **18** 1

Rowe, W P; Huebner, R J.; Gilmore, L K; Parrott, R H, and Ward, T. G (1953): Isolation of cytopathogenic agent from human adenoids undergoing spontaneous degeneration in tissue culture, *Proc Soc Exper Biol & Med*, **84** 570

Sabin, A B. (1959): Reoviruses, a new group of respiratory and enteric viruses formerly classified as ECHO type 10 is described, *Science*, **130** 1387

Vilches, A, and Hirst, G K (1947) Interference between neurotropic and other unrelated viruses, *J. Immunol*, **57**.125

Weinstein, L. (1955) Failure of chemotherapy to prevent the bacterial complications of measles, *New England J. Med*, **253** 679

Chapter Two

ANATOMIC AND PHYSIOLOGIC ASPECTS OF ACUTE RESPIRATORY DISEASE AND PNEUMONIA IN RELATION TO MANAGEMENT

INTRODUCTION

There is no time in the practice of medicine when we need to apply our knowledge of anatomy and physiology more than at the bedside of a patient acutely ill with pneumonia. This applies at all ages, but certainly it is highly critical in infancy. The baby's lung is like the baby's hand—it is there in all its parts, but is absolutely small! This simple fact presents many problems. No attempt will be made to present the subject from the point of view of the anatomist or physiologist, but rather from one clinician to another. What phases of these basic subjects can we use at the bedside of the sick patient? The physiologic aspects of some of the commonest symptoms, such as cough, dyspnea, cyanosis, and chest pain will be discussed

PHYSIOLOGY

The primary function of the pulmonary system is one of ventilation In order to do this job well, there must be no obstruction to the ingress and egress of air. The secondary function of the lung is to maintain proper tensions of carbon dioxide and oxygen which control to some extent the acid-base balance of the blood. This latter phase will not concern us appreciably as little or no significant deviation of acid-base equilibrium occurs in the blood of most patients with pneumonia. Most of the problems relate to ventilation, as the function of all of the organs and tissues of the body depends on oxygen Ventilation in the case of human beings means that air * must move in and out of the lung, leaving behind its oxygen, which is only about one-fifth of the total volume—the remainder of the air must be moved out to make room for the next load containing oxygen to move in. This latter process takes time and in the case of oxygen lack or air hunger, the respiratory rate is stepped up and respirations become rapid and shallow in an attempt to get sufficient oxygen to the blood and tissues

ANATOMY

The lung of the newborn infant is not a miniature of the adult lung, according to Engel (1947) and Looslı (1959). The respiratory units with their small, shallow alveoli are incompletely developed The elastic fiber system, too, so im-

* Content of inspired air is as follows

Nitrogen (N_2)	79 03%	596 45
Oxygen (O_2)	20 93%	158 25
Carbon dioxide (CO_2)	0 04%	0 30
Aqueous vapor		5 00
		760 00 mm Hg

portant in lung function, is incompletely developed in the newborn. After birth the lung grows by the formation of new respiratory units (Engel, 1947) *and the individual enlargement* of the alveolar ducts, sacs, and alveoli (Loosli, 1959).

The knowledge of the finer structure of the respiratory system which conducts the interchange of gases is most important if we are to appreciate fully what goes on in the presence of disease The actual ventilation takes place at the respiratory bronchiole and beyond. The tracheobronchial tree functions *primarily as a tube for conveying gases. It also serves to eliminate* foreign materials from the lower pulmonary tree by means of its secretions and ciliary action. *The secretion prevents drying* of the delicate membranes lining the air passages.

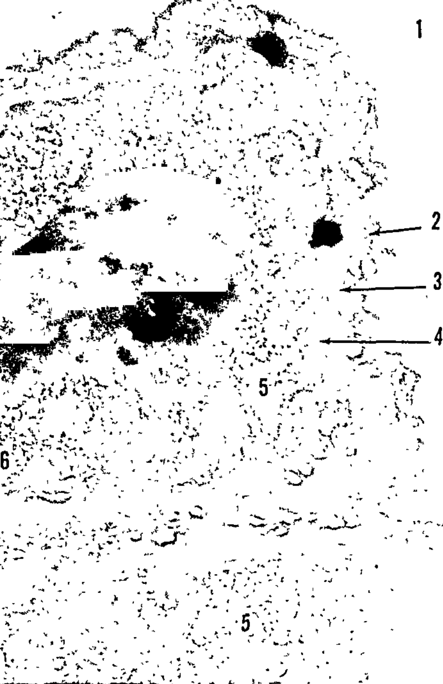
The respiratory bronchioles with the alveolar ducts, the alveolar sacs, and pulmonary alveoli make up the primary unit. Approximately half a dozen alveolar ducts arise from respiratory bronchioles, from which alveolar sacs come off and form from two to three alveoli One of the most critical areas *is the structure of the alveolar wall where the actual exchange* of gases takes place With ordinary light magnification the alveolar wall separating the air from the capillary lumina is extremely thin and appears to consist only of the capillary lining cells with the surrounding connective tissue fibers and ground substance (Loosli, 1938). Electron microscopic studies by Low (1953), Policard (1956), and others have revealed *the alveolar wall to have three layers consisting of* (1) capillary endothelium, (2) basement membrane, and (3) cytoplasmic layer of cells covering the surface of the alveoli (see Fig. 5, p. 30) The origin of the cells giving rise to this cyto*plasmic layer is still a subject of study*

The relationship of the alveolar membrane to *capillary* is essential not only for an understanding of the biochemical aspects *of respiration but also for appreciating* the symptoms and signs of disease which alter the character of this layer.

thus interfering with the flow of vital substances There is a generous distribution of lymphatics which drain the lower pulmonary units and appear to be important clinically in that absorption from these areas may cause the high fever so characteristic of pneumonia. The tracheobronchial tree, which is lined with columnar epithelial and secreting cells, allows for very little absorption; this accounts for the afebrile nature of patients with bronchitis per se When the patient has a fever we must look for inflammation in the upper passages or in the most peripheral areas of the pulmonary system.

VENTILATION

The ventilating process is essentially a passive one, the ingress and egress of air depending primarily upon pressure differences existing between atmospheric and intrapulmonary air. These differences are produced by expansion and contraction of the thoracic cage. With each inspiration the ribs move upward, increasing the lateral diameter of the chest, the diaphragm descends, and the sternum is elevated. The unequal enlargement of the thoracic cavity allows for less expansion in the apical areas than occurs in the lower portion of the lung. With normal breathing, of course, maximum gaseous exchange does not take place, and only about one eighth of the total potential aerating ability occurs at any one time. This normal exchange is referred to as tidal air and amounts to approximately 500 cc during quiet breathing in the adult The inspiratory reserve is that amount which we can inhale in addition to the tidal air if we make a maximal inspiratory effort This is approximately 1500 cc over the tidal air. The expiratory reserve is the quantity a person can blow off following tidal expiration, and is similar to the "inspiratory reserve" in amount—about 1500 cc An additional 1500 cc of residual air remains following a maximal expiratory effort. The vital capacity is the sum of the tidal, inspiratory, and ex-


1
2
3
4
5
6
5

piratory reserves and totals approximately 3500 cc. Functional residual air refers to the amount remaining in the lungs at the end of normal expiration which includes the expiratory reserve plus residual air. In Figure 6 the various compartments have been diagrammed simply to show their relationship in pulmonary activity.

Oxygen is transported in the body by the intravascular fluids and cellular elements, the most important component of which is hemoglobin in the erythrocytes. Ordinary saturation is approximately 95 per cent. It is affected directly by the tension of oxygen, carbon dioxide, the temperature, and pH, all of which are concerned in the chemical reaction of hemoglobin with oxygen. It is this loose chemical association that allows the red cells to pick up oxygen in the lungs and dispose of it in tissue capillaries. An exchange of CO_2 occurs in between the tissue capillaries and the tissues themselves, in which area the CO_2 tension is 46 mm Hg as compared with 40 mm Hg arterial tension in the lungs. When hemoglobin is oxygenated, the acidity increases, which in turn enhances its affinity for CO_2. This factor is important in maintaining a continuous oxygen–carbon dioxide exchange.

Before going into symptomatology, a few definitions of normalcy might be helpful. Normal breathing is referred to as *eupnea* and is simply made up of an active inspiration and a passive expiration. With exercise or exertion the gaseous volume of exchange increases; this increase is called *hyperpnea*. *Tachypnea* represents an increase in the respiratory rate alone, with increases of volumetric exchange. The temporary respira-

---

Figure 5. Electron microscopic photograph of normal adult lung of man showing the structure of the alveolar wall × 29,500. (1) Alveolar space, (2) cytoplasmic covering, (3) basement membrane, (4) capillary endothelium, (5) capillary space, (6) red blood cell. (Courtesy of Drs. Clayton G. Loosli and Richard F. Baker, University of Southern California School of Medicine.)

tory arrest that often follows hyperventilation is called *apnea.*

The most serious disturbance in respiratory rhythm has been called Cheyne-Stokes respiration, which consists of a series of respiratory efforts, progressively increasing both in

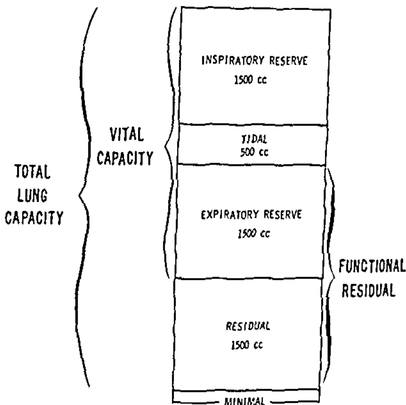


Figure 6. Diagrammatic representation of the various compartments of air in the normal process of pulmonary ventilation (Medical Illustration Service, Veterans Administration Hospital, Long Beach, California)

rate and volume, with a passive expiratory phase This cycle diminishes to the point of apnea and although it may occur naturally, it ordinarily indicates serious disease Certain drugs and illnesses, such as congestive heart failure, renal disease,

increased intracranial pressure, pneumonia, and bronchial asthma may be responsible for this type of breathing. Biot's respiration is characterized by hyperpnea and apnea which occur irregularly

DYSPNEA

This term refers to difficult or labored respirations regardless of whether or not the patient is conscious of his own difficulty. It is caused by any disturbance—mechanical, chemical, or nervous—in the control of breathing The commonest, simplest form follows exercise and usually implies varying degrees of hypoxia It is extremely important clinically to evaluate dyspnea as it is probably the earliest sign of oxygen deficiency, preceding more obvious signs such as cyanosis. In any particular case, dyspnea may be of a neurogenic nature and be wholly functional such as the type which may be related to severe pain in a visceral organ or an extremity Increases in pulse and respiratory rate may be the first indications of impending hypoxia

Disease in the respiratory passages may obstruct the normal pulmonary ventilating mechanisms. Such obstructions, as a rule, are due to pathologic swellings, growths, and possible foreign bodies A barrier may result from fluid as seen in pulmonary edema, from various forms of exudate as occur in association with pneumonia, and from chronic changes as seen in pulmonary fibrosis The extrapulmonary causes of hypoxic hypoxia, which rarely must be differentiated, are various forms of congenital heart disease in which there is a venoarterial shunt preventing sufficient aeration of circulating erythrocytes

COUGH

The lungs are relatively silent organs, but one of the earliest and most valuable symptoms may be cough which is produced

by closure of the glottis with a subsequent forceful expiratory effort. Sensitive points are found in the tracheal bifurcation and in laryngeal areas almost anywhere along the epithelial lining of the bronchial tree. Particles are moved out of the respiratory passages by ciliary activity, peristaltic movements, and coughing. Air or fluid, particularly in the pleural areas, often initiates the cough reflex, indicating their presence. In acute inflammatory conditions such as pneumonia, cough is initiated by irritation and excess fluids which result from the inflammatory process. Drainage from the nasopharyngeal areas will induce coughing, particularly when it passes the epiglottic barrier.

Postural drainage has been found to be helpful in preventing upper respiratory inflammatory fluids from entering the middle and lower pulmonary passages. One of the most effective ways to treat cough in infants is to place the baby in the prone position, following which puddling of mucus often occurs about the face There are many types of cough, but the louder, rough coughs are usually associated with inflammation in the pulmonary tree as opposed to the little hacking types of cough which are often on a neurotic basis Spasmodic coughing is often characteristic of pertussis, and a painful cough may indicate pleuritis Wheezing is usually related to forceful expiration.

CYANOSIS

This relates to the bluish-gray color of the skin which occurs in the presence of reduced hemoglobin It is the most definite indicator of hypoxic hypoxia and is not ordinarily seen in anemic hypoxia due to insufficient hemoglobin The bluish color is related directly to the absolute amount of reduced hemoglobin in the capillary blood Clinically, then, we may see dyspnea without cyanosis and the opposite also may obtain In general, heart disease and arteriovenous shunts

may be associated with severe cyanosis with little dyspnea. This sign will be discussed further in the following paragraphs concerned with pneumonia.

CHEST PAIN

There are no pain fibers in the lung parenchyma or visceral pleura. Pain is most commonly related to lesions which involve parietal pleura and is aggravated by deep respiratory movements. As a rule, there is little relationship between severity and the extent of the lesion. Central diaphragmatic pleural pains may be referred to cervical 3, 4, and 5 in the neck region, and peripheral diaphragmatic pain may be referred to the abdomen and lumbar regions. In pneumonia, patients commonly present acute abdominal findings suggesting an acute surgical condition. Certain pains in the chest may be related to myositis and neuritic conditions such as those produced by the herpes zoster virus. Probably the commonest forms of chest pain in adults are related to disease in the coronary arteries One must be constantly aware of abdominal conditions that may be referred to the chest, such as gallbladder disease.

PATHOLOGIC PHYSIOLOGY OF PNEUMONIA

In the early stages of pulmonary inflammation, unoxygenated blood may reach the aorta, but following consolidation of various areas little blood is circulated through them The advancing area of edema interferes with the normal diffusion rates and shallow respirations follow. Bronchiolar obstruction may lead quickly to hypoxia, with complete or partial obstruction of certain small passages, areas of atelectasis and emphysema develop quickly. The blood then courses through capillaries in which no oxygen may be available In acute bronchiolitis in infancy, air trapping with signs of overaeration and depressed diaphragm is a very common roentgen finding These

babies are dyspneic and are ventilating very poorly. Cyanosis is a common finding in pneumonia and is usually visible when the oxygen saturation falls below 85 per cent. In the anemic individual or in patients suffering from shock it may fail to be a striking sign Other symptoms, such as delirium, tachycardia, and dyspnea, should indicate the need for oxygen Toxemia and hypoxia may stimulate proprioceptive reflexes in the lung which tend to increase the volume of breathing. Vital capacity is sharply reduced, and total lung capacity and functional residual air are also diminished.

OXYGEN THERAPY

The extreme value of increased oxygen intake in patients with pneumonia has been shown to be beyond question for many years. Atmospheres containing 50 per cent oxygen will raise arterial oxygen saturation to near normal levels and other signs of improvement occur, such as slowing of the pulse, disappearance of or diminished cyanosis, diminution of delirium, and lowered fever in many patients. Dyspnea may be partially or completely relieved The primary purpose of oxygen therapy is to maintain or improve the function of the lung with respect to the absorption of oxygen in order to prevent damage to the various organ systems during the critical stages of disease In the presence of widespread pulmonary disease, such as seen in infants with bronchiolitis, it is a most valuable and necessary therapy

Pulmonary capillaries are dependent for their oxygen supply on alveolar oxygen tension. Poor ventilation in a splinted area may lead to local hypoxia and corresponding local edema because of the increased permeability of lung endothelium in the presence of a diminished supply of oxygen

When oxygen therapy has been decided upon, the method of administration and concentration of oxygen are vital considerations Concentration should be sufficient to overcome

arterial hypoxia. This may become a matter of clinical judgment which may best be determined by careful observation and good nursing. Studies indicate that arterial hypoxia may be overcome in the majority of patients with pneumonia by an atmosphere containing 50 per cent oxygen. However, higher saturations may be necessary in severely ill patients, and a careful watch of the oxygen concentration may be lifesaving. When high concentrations are required, long-continued use of oxygen must be carefully watched and guarded against because of the dangers of irritating and toxic effects referred to as oxygen poisoning. Oxygen tent concentrations of 70 per cent as a rule may be continued for long periods of time. Simple, clear plastic oxygen tents have proved extremely useful and valuable. Oxygen therapy is frequently combined with a humid atmosphere in the treatment of infants with croup and signs of laryngotracheobronchitis. Oxygen, as a rule, may be discontinued following the return of the temperature and pulse rate to normal. Constriction of the bronchial tree may occur in patients with various forms of atypical or virus pneumonia. An element of bronchospasm may be associated, and frequently the use of epinephrine (Adrenalin) followed by steroid therapy may be lifesaving. The use of aminophylline is often followed by striking diminution in cough and dyspnea.

Pulmonary function studies will not reveal where or what the lesion is or its very existence if it does not interfere with function. However, they provide an important complement to the history, physical examination, and radiologic, bacteriologic, microscopic, and pathologic studies. Although the primary function of the lung is a singular one, that of gaseous exchange, a number of processes are involved. (1) Ventilation—this includes both volume and distribution of the air ventilating the alveoli. A sufficient volume of inspired air must reach the alveoli and this air must be distributed evenly to hundreds of millions of alveoli in the lungs (300,000,000). (2) Diffu-

sion—the process by which O_2 and CO_2 pass across the alveolar capillary membranes. (3) Pulmonary capillary blood flow—which must be adequate in volume and must be distributed evenly to all the ventilated alveoli. Mechanical factors are of great importance because adequate pulmonary gas exchange is achieved only by the increased work of the respiratory musculature, and it is for the relief of this effort that much of the therapy is directed.

The work required by the right ventricle in pumping blood through a restricted pulmonary vascular bed may be of critical importance. The value of pulmonary function tests is great indeed and will play an ever-increasing role in the adequate management of the patient. They are as important to the practice of good medicine as hepatic, renal, cardiovascular, and neuromuscular function tests not only in diagnosis but also in guiding therapy of patients with cardiopulmonary disorders. Pulmonary function tests have proved to be invaluable in establishing physical and measurable data in patients who have suspected pulmonary disability.

MANAGEMENT OF ACUTE RESPIRATORY TRACT INFECTIONS

The practical problem of the treatment of acute undifferentiated respiratory disease, when to treat and what drug or drugs to use, faces the practitioner daily. Unfortunately, these important questions cannot be answered with a few concise and well-chosen words; yet we must make therapeutic decisions if we are to practice good medicine In the next few paragraphs an attempt will be made to summarize the problem and to present a logical approach to treatment

Every practical effort should be made to establish a working diagnosis. A mere guess that it sounds like a "virus infection," "tonsillitis," or "flu" is not as a rule sufficient to initiate a logical program of treatment It may be impossible to do

more than guess and offer a working diagnosis to the patient, but a thorough scientific approach to an etiologic diagnosis, even though it be a guess, should be made. This does not mean that we have to start drawing blood, making throat and stool cultures for bacteria or viruses, but it does mean that we should make the most of the practical clinical methods available to all well-trained physicians. We sometimes forget the importance of a good history and hurry through a cursory physical examination. These interrelated clinical procedures form the basis for a good working diagnosis which may or may not be confirmed later in the laboratory. The history, besides revealing the prominent symptoms, should include epidemiology, history of exposure to disease, recent family illnesses, and their characteristics Nearly all of the acute respiratory illnesses will occur in family epidemics. A story of previous illnesses in the patient and past preventive measures is essential Physical examination should be thorough because it provides a sound base for future observations, it rules in or out complications which may or may not require immediate treatment, and it indicates further diagnostic procedures which may or may not need to be performed

The most fundamental aid to a logical approach to diagnosis and treatment is a thorough working knowledge of the etiologic possibilities and the diseases caused by them. It is important to remember and constantly keep in mind that bacteria account for a relatively small part of all primary respiratory tract infections The group A *beta hemolytic streptococcus* is the only common cause of acute nasopharyngitis due to bacteria. There are just two very practical steps to take when the history and physical examination suggest that this organism might be responsible for the patient's illness The white blood count is nearly always elevated above 12,000 cells with an increase in polymorphonuclear cells A simple nose and throat culture will go a long way toward establishing

a practical working diagnosis. Penicillin is the drug of choice, but in case of sensitivity another suitable antibiotic should be selected. The dose will depend on the physician's judgment; the age and severity of illness usually determine the method of administration. If the diagnosis is well established, at least ten days of therapy are indicated.

By far the commonest causes of acute respiratory diseases are nonbacterial and for all practical purposes must be considered as presumably viral. This fact alone puts a high premium on a practical working diagnosis, because if no evidence of a bacterial infection or complication exists specific drugs should not be given. When bacteria are causing disease it will usually be obvious by the symptoms and signs, at which time a wise decision may be made regarding therapy. Prevention of complications may rarely be a prime consideration, but emergence of antibiotic-resistant organisms can cause complications in treated patients with increasing facility, and we should not delude ourselves or our patients about the possibility of prevention Routine use of antibiotics or sulfonamides is not recommended for prevention of complications. Rather, early detection of complications is preferable

With rare exceptions, there is no specific therapy for most of the nonbacterial causes of acute respiratory disease Psittacosis or ornithosis may cause an illness indistinguishable from many that are caused by other primary respiratory viruses This disease should be treated with the tetracycline drugs or penicillin in large doses Q fever may cause an acute influenza-like illness which should also be treated with tetracycline or chloramphenicol if the diagnosis is clearly established and the patient is severely ill Other known bacterial and viral causes must be considered in the differential diagnosis These rarely include fungal infections such as coccidioidomycosis, histoplasmosis, and leptospirosis.

The next logical step toward an etiologic approach to diagnosis and treatment is an acquaintance with the new viruses that are rapidly filling in the large gaps in our etiologic knowledge of respiratory tract infections. The influenza viruses, A, B, and C, the new *myxoviruses* which cause para-influenzae 1, 2, and 3, the new *adenoviruses*, and the *enteroviruses* are all responsible for varying amounts of acute respiratory disease. Nearly all of these viruses are characterized by their tendency to produce epidemics either in an institution or the family. *Adenoviruses* cause typical exudative tonsillitis, pharyngoconjunctival fever, acute respiratory disease (ARD), epidemic keratoconjunctivitis, and simple follicular conjunctivitis. The newly named *enteroviruses* may cause acute respiratory tract infection; they include Coxsackie groups A and B, *polioviruses*, and ECHO viruses. These latter diseases occur commonly in the summer months Vesicular pharyngitis or herpangina is caused by several of the Coxsackie A viruses and may usually be diagnosed by the characteristic appearance of gray vesicular lesions in the pharyngeal areas *Polioviruses* may cause mild respiratory disease, and a few of the new ECHO viruses have also been shown to be etiologically related to acute respiratory disease. None of these diseases responds to any known antibiotic.

In the last analysis, great clinical judgment is required as the overwhelming majority of the respiratory illnesses which we are called upon daily to diagnose and treat defy diagnosis early and usually do not require specific treatment If, however, we evaluate our patients critically, approach the diagnosis etiologically, and give specific treatment only when we have an indication, we shall be offering an invaluable service to those who call upon us for help Sir William Osler aptly said over a half century ago "One of the first duties of the physician is to educate the masses not to take medicine "

Chapter Three

MYXOVIRUS INFECTIONS, INCLUDING INFLUENZA AND OTHER NEW RESPIRATORY VIRUS DISEASES

Proposals of the International Nomenclature Committee concerning the classification of viruses were made at the International Microbiological Conference held in Rome (1953). An acceptable compromise was sought between Linnaean and non-Linnaean binomials, and the latter was decided upon for the time being. Animal viruses would be known by group names and carry the suffix "-virus," and thus no attempt at classifying would be made in advance of adequate knowledge The generic (or equivalent) level would be the term used for various groups of viruses, such as *polioviruses*

THE MYXOVIRUS GROUP

The *myxovirus* group, as formulated in 1955, includes the following members. *M. influenzae-A, influenzae-B, influenzae-C, multiformis, pestis gallis, parotitidis,* all having a special affinity for certain mucins. Several new viruses have come to light recently with characteristics which render them appro-

priate for inclusion in the *myxovirus* group. These are the hemadsorption viruses (types 1 and 2) and the croup-associated (CA) virus, which will be referred to in the future as *M. para-influenzae 1, 2,* and *3* (see classification, pp. 22, 23). A brief description of the group includes morphology of the viruses that take the form of spheres, ranging in size from 60 to 200 mμ (see Fig. 7). They are very stable at –76° C. These viruses adsorb onto the surface of red blood cells of fowls and some vertebrates, causing agglutination of the cells The adsorption and hemagglutination may be inhibited by certain mucoproteins, and distinct antigenicity of various members of the groups can be shown by complement-fixation, hemagglutination-inhibition, and neutralization tests

Natural transmission is by means of secretions of the respiratory tract of infected hosts. The virus inhabits the respiratory passages of mammals or birds in which generalized infections occur with viremia. Infections may be inapparent or overt because of acute inflammation of the respiratory tract. This group of viruses will infect the amniotic cavity of fertile hen's eggs, and after adaptation produce transmissible pneumonia in mice and hamsters The following discussion will be limited to the influenzas A, B, and C and the para-influenzas, types 1, 2, and 3 *M multiformis* is referred to very briefly as the cause of Newcastle disease

Epidemiology of Influenza

Although no one knows when pandemic influenza was first recognized, Hirsch (1883) records the date as the year 1173 Since then pandemics of influenza have occurred at irregular intervals, the most outstanding having occurred in 1918 The most recent world experience with this disease occurred in the last three months of 1957 and first three months of 1958, and it is commonly referred to as Asian influenza. Although pandemic influenza connotes a degree of severity, technically

it is concerned primarily with world-wide distribution of this illness, whereas epidemic or interpandemic influenza may refer to more localized outbreaks, usually of a milder nature Robert Johnson (1793) described the details of the influenza epidemic of 1789 and called attention to the speed with which influenza spread from one locality to another. Although the attack rate was high he referred to the mortality as low, unless patients were treated injudiciously. It seems clear that Johnson recognized the infectiousness of influenza, but had difficulty accounting for the rapid spread of this disease at a time when travel was very limited He concluded that the disease "often does arise from some vicious quality of the air or exhalation in it, as well as from a matter arising from the body of a man labouring under disease"

The first pandemic to occur in the bacteriologic era was in the years 1889–90. Influenza in this pandemic involved the whole world in a matter of a few months, occurring in widely scattered areas at the same time Starting in European Russia and Siberia in early October, by November the epidemic was prevalent over most of Europe and in December was widespread in England and America This pandemic, although not carrying the high fatality rate which the world experienced in 1918, according to Vaughn (1921) the 1889 pandemic was identical with the 1918 disease in practically all of its manifestations Pfeiffer (1892–93) discovered an organism which later became known as the influenza bacillus and was attributed by him and many other bacteriologists and clinicians for years as the cause of influenza.

The pandemic of 1918 still remains the most severe experi-

Figure 7. An electron microscopic picture of influenza virus, type A showing the spherical shape of the individual virus particles, which are magnified approximately 100,000 times (Courtesy of Dr Robley Williams, Virus Laboratories, University of California, Berkeley)

ence with this disease that world history has recorded. The earliest manifestation of the disease was in Spain, where it appeared suddenly and subsided without leaving a trace after running a brief course. In April, 1918, similar epidemics appeared in England, France, and the United States, particularly among military personnel An epidemic was also recorded in the spring of 1918 in Japan and China, which was considered as a mild three-day fever. The spring epidemic was recorded as the first wave and was mild compared to the case fatality and severity of the second wave which occurred in the fall of 1918. The second wave appeared in many parts of the world at the same time. It spread rapidly in the military camps and neighboring civilian communities and by October was world-wide in its distribution. Although the majority of the attacks of influenza were of a relatively mild nature as experienced in the spring epidemics, two serious forms of the disease made their appearance. The first of these was an illness characterized by a sudden onset with acute pulmonary inflammation resulting in lung edema, cyanosis, and death in a few days The second type developed on the fourth or fifth day of what appeared to be an ordinary illness and took the form of bronchopneumonia resulting in death or a long convalescence.

Again, wide discrepancies in the epidemiology appeared Boston and Bombay had their epidemic peaks in the same week, while New York, only a few hours by train from Boston, did not have its peak until three weeks later Experiments set up to prove the contagiousness of influenza failed to do so Human volunteers who were heavily exposed to patients in the acute phase of the disease failed to become ill It is difficult to explain the failure of these transmission experiments other than to assume that the volunteers had a subclinical illness which provided sufficient immunity to protect them from a challenge experience Shope (1958) emphasizes the tremen-

dous amount of work which was put forth to prove or disprove the importance of the influenza bacillus of Pfeiffer as the cause of influenza, and after years of work considerable doubt still existed as to its significance in this disease. Although many workers considered that a virus was probably responsible for influenza, little evidence was gained in the 1918 experiences to prove this contention The actual proof of the cause of human influenza was not forthcoming until the work of Smith, Andrewes, and Laidlaw in 1933.

Shope's (1931) studies with swine influenza are extremely important even today in the fundamental pathologic physiology of this disease. Lewis and Shope (1931) found an organism in swine which they identified as the *Hemophilus influenzae bacillus suis*. They were able to recover this organism consistently from sick swine, however, when presented in pure culture to susceptible animals no illness occurred Shope (1931) soon discovered that the bacillus was not the sole cause of swine influenza and that a filterable agent was responsible for a mild illness which was true swine influenza. When combined with the bacillus, the two agents acting in concert produced the more serious and fatal forms of swine influenza

Following the discovery of the human agent in 1933, a striking similarity with the swine agent was quickly demonstrated. The hypothesis was then developed that there was a relationship of the swine influenza of 1918 to the human pandemic disease, and although direct proof does not exist for the causative factors in the pandemic of 1918, serologic tests from patients in later epidemics revealed that neutralization of the swine influenza virus was possible. Shope (1936) feels that one is warranted in speculating that the second wave of the 1918 influenza pandemic had as one of its etiologic components a virus that was serologically closely related or iden-

virus that is similar to the type A human strains which we now recognize as major factors in the etiology of this disease.

In discussing the immunologic relationships between the first and second waves of various epidemics, Shope (1958) pointed out that Navy personnel who survived an attack during the spring epidemic in 1918 escaped infection during the second wave. He concluded that mild attacks early in the year conferred immunity against the fatal type of the disease which appeared later.

The most recent epidemic, now referred to as Asian influenza 1957, apparently started late in February of 1957 in southwest China, spreading to Yunnan Province in early March, from which it spread throughout much of the Orient, appearing in the United States by the middle of May Military personnel arriving in this country apparently were responsible for small civilian outbreaks which occurred during the summer months particularly in camps and at conventions A wide seeding took place throughout the United States as a result, but the epidemic did not develop until early in October Asian influenza was found to be due to a type A virus but quite distinct from any previous type A viruses which were readily available. This indicated that the immunity in the world was at a very low level, and theoretically the situation for a pandemic existed. The rapid spread in the Far East as well as some mortality that occurred among young adults in the early phases of the epidemic indicated that this epidemic should be taken seriously The first wave involved most of the United States between October and the latter part of December, at

mately three days with few complications occurring. Although a real mortality was associated with these mild epidemics, it failed to stand out in any particular locality, but did tend to appear in certain age groups when large statistical surveys were made. The national figures gathered from 108 cities throughout the United States showed a sharp increase in mortality during the epidemic period. This is strikingly illustrated in Figure 8, which clearly demonstrates the two phases

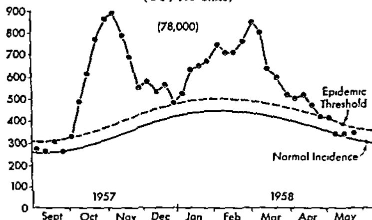


Figure 8. [illegible]

of this past epidemic. During January, 1958, the mortality and morbidity again increased, reaching a peak in February and dropping off again during March. This wave, instead of becoming more severe, was probably less severe than the initial one, but it did carry a surprisingly high mortality. It was particularly striking among the very young and aged who

may well have escaped infection in the first wave of the epidemic. Surgeon General Burney said statisticians estimated between 30 and 50 million Americans suffered Asian-variety influenza and the death of upward of 78,000 could be directly attributed to the disease. Eighty-five per cent of the deaths occurred in individuals over 55 years of age.

A most heroic effort was made on the part of the government, and with the cooperation of the pharmaceutical manufacturing concerns, vaccines made from the Asian strains of influenza were used rather widely. There is some evidence that the vaccine may have played a significant role in controlling the severity of this pandemic. The availability of antibiotic therapy also probably played a most significant role in controlling or preventing the serious complicating forms of this disease The common secondary invaders undoubtedly were held in check by the rather widespread use of antibiotics. Shope (1958) emphasizes that too little experience is as yet available with respect to the *Hemophilus influenzae* bacillus; should it become a common invader in an epidemic of influenza, it is still questionable as to whether or not it could be controlled adequately. A specific vaccine would appear to be the most effective form of control for a particular epidemic or pandemic of influenza.

Herrmann and associates (1958) reported 23 deaths which occurred in the vicinity of Denver, Colorado, during the height of the last Asian influenza epidemic, October 3–20, 1957 They emphasized that sudden death was a feature of the patients whom they studied, although their series was small, as many as four infants were included in the first three months of life, and for this limited age group this series represents an extremely high mortality Only five or six patients were involved in any other 10-year period Another striking feature of this epidemic has been the occurrence of varying reports of encephalitis which appeared to be closely allied to the epidemic Although

many of these reports are not completely confirmed by isolation of the agent from the central nervous system, virus isolations and significant serologic increases are being reported, and it seems possible that in very rare instances the influenza virus is capable of producing an acute encephalitis, often terminating in death.

Asian strain of virus was isolated from extrapulmonary tissues from three patients who died from influenza by Kaji, Oseasohn, Jordan, and Dingle (1959) They suggest that this finding indicates the occurrence of viremia in overwhelming influenza in man Hamre and co-workers (1956) found virus in the blood and extrapulmonary tissues of animals, and suggested that it occurred in man Fatal cases of Asian-strain influenza associated with encephalopathy have been reported by Flewett and Hoult (1958), who were successful in isolating virus from both brain suspension and a pool of lung and trachea from one case

Clinical Features

The onset of the disease is usually sudden Infants and children with influenza frequently have fevers of 39 4° to 40 6° C on the first day of illness Signs of toxicity and marked lassitude are the principal symptoms, and older patients often complain of sore throat Podosin and Felton (1958) reported the clinical picture of Asian influenza which occurred at the Fourth National Boy Scout Jamboree held at Valley Forge, Pennsylvania, in July, 1957 Fever, headache, cough, and sore throat were the most common complaints. They also recorded malaise and prostration in a fairly high percentage of patients They enumerated other organ systems which were involved apart from the respiratory passages, emphasizing myalgia, abdominal pain, earache, and other minor complaints

On physical examination hyperemia of the nasal pharyngeal

membranes was the most striking finding, occurring in 76.5 per cent of the juvenile patients. Mild conjunctivitis and rhinitis were also frequent symptoms. Conjunctivitis was recorded in 38 per cent of the patients in the Boy Scout epidemic. Over 20 per cent of the patients had abnormal chest findings which were not necessarily related to the presence of changes in the roentgenograms. Fever occurred in 95 per cent of the patients with an average highest temperature of 39° C. In an epidemic in infants and children due to type A influenza virus, which occurred in 1943 (Adams *et al.*, 1944), a high, irregular fever was recorded as a constant finding in all of the proved cases. Irregularity of fever was striking, including a biphasic type of temperature curve in many of the patients If complications did not intervene, the febrile course often terminated by crisis.

The clinical laboratory studies in the infant and children series failed to reveal the presence of a leukopenia except in one patient The average total white count was 9000 per cubic milliliter at the time of the acute onset of the disease In Podosin and Felton's study (1958) on teen-age boys a normal white count was recorded in 63.5 per cent of the patients Leukopenia was found in about 20 per cent of the patients studied. Roentgenograms of the chest were abnormal in 7 5 per cent. Although the findings of increased bronchovascular markings were frequent, these were not included among the patients with abnormal findings, which were confined to pulmonary infiltrations These cleared rapidly with no serious sequelae A high incidence of bronchial asthma was found in this group of patients, all of whom had a previous history of asthma The percentage of pulmonary complications was greater in the asthmatic patients and their hospital stay was prolonged

Loosli, Hamre, and Warner (1958) reported on epidemic Asian influenza in naval recruits The clinical findings were

those of epidemic influenza, symptoms occurring abruptly with high fever, chilliness, malaise, headache, myalgia, mild cough, scratchy throat, and mild rhinitis. Occasionally patients complained of nausea without diarrhea. Physical examination revealed flushing of the skin over the face and chest with mild conjunctivitis The throat was diffusely red and coughing was not pronounced There were no abnormal pulmonary findings. The explosive spread of the infection among the recruit population was indicated by the rapid daily increase in admissions for about a 16-day period, following which it gradually dropped off. This was an unusual epidemic in that it occurred in summer months in San Diego from approximately the middle of June to the first week in July, 1957. The attack rate was extremely high involving approximately 75 per cent of the recruit population, which were either admitted or treated in the dispensary for acute respiratory illnesses from June 8 to July 5 The cause of this epidemic was confirmed by throat washings and blood studies Asian influenza virus was isolated from 57 per cent of the patients, and 80 per cent of the paired sera showed fourfold or greater complement-fixing antibody rises with the type A Japan 305 57 as antigen, indicating that essentially all rises were due to this strain

Laboratory Diagnosis

A final diagnosis of influenza is dependent upon information which we must attain in the laboratory, where virus isolations and serologic responses may be clearly demonstrated There are many other diseases which can closely simulate influenza, as we are attempting to point out in this book, but at the same time we recognize that during an epidemic the *great majority* of patients who present the classic symptom picture are suffering from influenza This fact has been demonstrated by blood studied in the past, and although an adequate explanation is not clearly evident, it seems possible that the phenomenon of

virus interference may play a significant role. In the San Diego study just referred to, 88 per cent of the patients had significant changes in their serum to establish the diagnosis.

In the epidemic of Asian influenza, the importance of the laboratory has been clearly demonstrated repeatedly. The cause of the epidemic was defined early, and found to be due to a new variant of the influenza virus, but definitely in the category of type A. It was quickly learned from antibody studies that the level of titer in the over-all population was extremely low. This indicated early that world-wide spread might be expected from this particular strain of virus. The WHO (World Health Organization) program for influenza responded quickly to this information, responsible military and public health service officials were alerted, and efforts toward the production of a vaccine were started at once.

Jensen and Hogan (1958) reported that results of laboratory tests in July indicated that strain A/Japan 305/57 was useful for complement-fixation tests only and that the hemagglutination-inhibition method was much less meaningful. However, following transfer of the virus to ferrets, the "animal line" virus was much more sensitive to the antibody in the hemagglutination-inhibition tests. This test may sound complicated but actually it is a very simple procedure stemming from the fact that chicken red cells are agglutinated by influenza virus This agglutination of red cells may be inhibited completely by antibodies in the serum of recovered patients, whereas early in the illness the serum has no inhibiting effect. Therefore, the hemagglutination-inhibition test is a simple, accurate way to determine whether the patient has had influenza

The laboratory has been able to confirm that all type A isolations obtained from various parts of the world since June, 1957, were closely related to the original strains of Asian influenza, and these appear to have replaced the pre-

viously prevalent strains referred to as A prime or the FM family. The International Influenza Center has studied over 200 isolations, and all have been readily typed as the Asian variety. The facility with which virus isolation can be made varies greatly, but depends upon the procedures used in collecting specimens and in shipping them to laboratories. The amniotic cavity inoculation of 11-day embryonated chicken eggs continues to be the method of choice for primary isolation. These isolations are tested against guinea pig erythrocytes to detect the presence of hemagglutinating virus. When the test is negative with chicken erythrocytes, certain strains may give a positive test with guinea pig red cells, and thus a specific virus may eventually emerge. A lack of specificity in antibody responses to influenza with complement-fixation tests has been known for many years. Jensen and Hogan (1958) point out that although the serologic diagnosis of influenza is frequently afforded by the CF (complement-fixation) technique, a significant number of cases will be missed unless the sera are also studied with the HI (hemagglutination-inhibition) test.

In the epidemic of Asian influenza, patients have responded by producing increased antibody titers against the older virus strains with no appreciable production of antibodies against the Asian strains. The viruses obtained from these cases, however, were always of the Asian variety. Therefore, Jensen and Hogan (1958) conclude that serologic diagnosis cannot be relied upon as a means of defining the infecting agent, but only as a means of defining a broader immunologic type. As indicated previously, the isolations from June, 1957, through November, 1957, in laboratories all over the world have been of the Asian variety only. In all probability, the older strains have disappeared from the scene, and strains related to the new Asian variety will be the prominent strains with which we shall have to contend in epidemics in the near future. It has been pointed out on several occasions that great shifts in the

antigenic composition of influenza viruses have occurred at least three times at intervals of approximately 10 years.

Pathology

Although records of influenza epidemics date from the twelfth century, little is known of the pathologic changes caused by the virus of influenza in man. MacCallum (1940) stated in the seventh edition of his textbook of pathology that "no one died of influenza alone without secondary infection with bacteria," and after extensive studies he and his associates reported that they were entirely uninformed as to the nature of any changes in the internal organs which may result from influenza as such. The most characteristic clinicopathologic feature in the proved epidemics of influenza in man has been acute pharyngitis. Francis (1941) stated that the virus of influenza exerts its initial and primary effect on the epithelium of the upper respiratory tract. This was also recognized by Bloomfield and Harrop (1919) in recording studies from the large pandemic of 1918. They reported: "Early in the course of the epidemic we noticed an unusual bright red appearance to the throat in most patients."

In 1946, Adams and associates reported the microscopic pathologic changes of the acutely inflamed human pharynx in an epidemic of proved influenza A infection. At the time they were unaware of any recorded pathologic changes in *man* in the uncomplicated disease. However, Francis and Stuart-Harris (1938) described the nasal histologic changes accompanying influenza infection in ferrets. A summary of their findings is as follows. "During the acute stage of infection the respiratory epithelium of the nasal mucous membrane undergoes necrosis with desquamation of the superficial cells and exudation into the air passages and an inflammatory reaction occurs in the submucosa." Influenza when artificially produced in the mouse is primarily a pneumonic process, but the cellular changes are

consistent with those observed in human pharyngeal tissues and exudate. The cellular exudate in the animals consisted of about two-thirds small mononuclear cells and one-third polymorphonuclear leukocytes. Nelson and Oliphant (1939) recorded damage to the bronchial epithelium with peribronchial infiltration chiefly by small mononuclear cells. Straub (1937) also expressed the belief that destruction of large portions of the bronchial epithelium is the most conspicuous feature of mice dying from influenza.

In studies (Adams *et al.*, 1946), swabbings of the pharynx were made in varying stages of the disease in an epidemic of proved influenza A infection. Pharyngeal smear biopsies were made by means of a dry cotton swab on a long applicator which was thoroughly rubbed over the posterior and lateral pharyngeal walls and promptly applied to glass slides. Over 300 specimens were studied from young adults and children suffering from acute influenza A infection. Control pharyngeal smears were made in a similar manner from young adults and children who were well at the time and also from individuals six months after the epidemic of influenza had ceased.

The pharynx appeared beefy red in the acute stage of the disease at a time when many of the patients complained of sore throat. The pharyngeal tissues appeared hyperemic, and occasionally bleeding was elicited by the swabbing procedure. Large sheets of epithelial cells were found as opposed to the purulent type of exudate which is so commonly observed with bacterial infections of the respiratory tract. A mononuclear exudate was the most singular pathologic change in the human pharyngeal exudate This type of cellular response is consistent with the pathologic changes recorded in other types of viral infections and of influenza in lower animals. McIntosh and Selbie (1937) found great increases in mononuclear cells in the alveolar walls of mice and ferrets which they studied. Francis and Stuart-Harris (1938), using large doses of in-

fluenza virus in ferrets, recorded a high degree of destruction of the epithelium of the respiratory tract; the exudate was chiefly polymorphonuclear. McCordock and Muckenfuss (1933) found the reaction occurred in accordance with the quantity of virus employed in experimental studies. The concentrated dose produced an acute hemorrhagic type of response with necrosis, whereas the more diluted dose produced a proliferative response with mononuclear cellular infiltration Francis and Stuart-Harris (1938) called attention to mononuclear infiltrations during the stage of repair and regeneration in ferret epithelium. Rivers (1928) similarly pointed out that acute inflammations occur in many viral diseases and that, if secondary infections do not intervene, the inflammatory process is usually characterized by infiltration of mononuclear cells.

In human beings a mononuclear exudate, made up mostly of small lymphocytes, histiocytes, and plasma cells, varied greatly in amount and was frequently mixed with a few polymorphonuclear cells, many of which were degenerating. Early in the course of infection the mononuclear exudate frequently represented the predominant response. Thirty-five individuals with definite positive serologic responses were studied in detail in order to attempt to quantitate the leukocytic reactions It was found (Adams *et al*, 1946) that 24 (68 5 per cent) of these patients had a predominant mononuclear exudate The quantitative evaluation of these smears was compared with the group of control subjects, 17 per cent showed a predominant polymorphonuclear response with no controls showing a mononuclear reaction The conclusions of these pathologic studies indicated that the most characteristic clinical pathologic feature of epidemic influenza was acute pharyngitis Although increased destruction of pharyngeal epithelial tissues was definite as compared with the control specimen, the single most important pathologic feature of the pharyngeal exudate of these patients with proved influenza was a mononuclear exudate,

particularly in the early phases of the infection. When a polymorphonuclear exudate occurred it frequently presaged the complicating secondary bacterial infection. Finally it was pointed out that a study of pharyngeal smears is helpful in the differential diagnosis of bacterial, fungal, and virus diseases involving the human throat.

Studies of a similar nature have confirmed the finding of a mononuclear exudate as the earliest pathologic change in the acutely inflamed pharynx of the patient with influenza In a report by Pierce and Hirsch (1958), inclusion bodies were found in patients with influenza viral infections. In their study of coughed-up sputum specimens from 30 patients with influenza, 26 were found to be positive for cells containing inclusion bodies. In studies of influenza A infection that occurred in an epidemic of influenza in Minnesota in 1943 (Adams *et al.*, 1944), we were unable to find an increase in inclusion bodies in the epithelial cells of the sputum and exudate from these patients as opposed to controls However, increased numbers of inclusion bodies occurred in presumably viral infections proved not to be influenza in infants and also in a few older individuals with primary atypical pneumonia. Pierce and Hirsch (1958) concluded that sputum cytology was valuable in the prompt differential diagnosis between viral and bacterial respiratory infections The same authors called attention, as we did, to small and large mononuclear cells seen during the initial influenza phase which changed when secondary bacterial complications occurred, at which time the leukocytic exudate became predominantly polymorphonuclear

Prevention

Davenport (1958a), director of the Commission on Influenza, Armed Forces Epidemiological Board, emphasized the severe impact of Asian influenza upon this country At the height of the epidemic in mid-October, 1957, the United

States National Health Survey, counting only patients confined to bed one or more days, reported that almost 12,000,000 new cases occurred within one week. Approximately *three times the normal expected death rate from influenza and* pneumonia occurred at the peak of the epidemic (see Fig. 8).

Vaccination appears to be the outstanding method for control of human influenza. To date, researches in the field of effective chemotherapy have failed to show much promise of controlling influenza viral infections. Russian investigators have claimed success with the inhalation of horse antiserum which undoubtedly carries a high risk of sensitization to foreign protein. Russian workers have also employed living-virus vaccines, *produced from attenuated strains, administered by* inhalation. These vaccines had the disadvantage of producing severe illness in children and had little protective effect unless the antigenic strains prevalent in the epidemic were employed The polyvalent vaccine was also limited by interference between virus strains when given to human volunteers

Killed-virus vaccine given by the parenteral route has been the main method of prevention employed in the United States Field trials which have been carried out since 1943 are reported in Table 2 and show the various types of influenza, including the 1957 Asian strains, the doses of vaccine that have been employed, and the protection ratios in the various studies. The Commission states that the effectiveness of the vaccine is clearly illustrated, pointing out that in the epidemic of *1943*, due to influenza A, *at least 3 6 times as many cases* occurred among the unvaccinated as among the vaccinated persons An even higher rate was accomplished with influenza B, which had a protection ratio of almost 13 In 1947, with the appearance of A-prime strains, the vaccine was *found to* be less effective When these strains were introduced into the vaccine good protection was achieved. The experiences with the Asian influenza vaccines have also shown effective protec-

Table 2 *

PROTECTION AGAINST INFLUENZA CONFERRED BY VACCINES DEVELOPED AND TESTED BY FIELD TRIAL UNDER DIRECTION OF THE COMMISSION ON INFLUENZAS

Year	Prevailing Type	Concentration of Vaccine	VACCINEES			CONTROLS			Protection Ratio †
			Number	Cases	Rate	Number	Cases	Rate	
1943	A	5,000 HU	5,806	114	1 96	5,776	408	7 06	3 6
1945	B	5,000 HU	1,150	10	0 87	2,150	241	11 21	12 9
1947	A'	5,120 HU	10,328	743	7.19	7,615	616	8 09	1.1
1950	A'	300 CCA	670	8	1 2	2,082	78	3 7	3 1
1951	A'	500 CCA	2,596	13	0 5	5,228	105	2 01	4
1952	B	700 CCA	207	15	7 24	430	83	19 32	2.7
1953	A'	750 CCA	5,994	57	0 95	5,527	316	5 7	8 1
1953	A'	750 CCA	2,616	16	0 61	4,865	135	2 77	4 5
1955	B	50 CCA Adj	2,000	43	2 2	2,000	70	3 5	2 2
1957	A'	750 CCA	1,188	11	0 92	1,216	62	5 1	5 5
1957	Asian	250 CCA Mono	916	20	2 18	1,448	55	3 79	1 7
1957	Asian	200 CCA Mono	775	46	5 93	806	121	15 01	2 5
1957	Asian	400 CCA Mono	649	12	1 73	1,238	65	5 25	3
		400 CCA Poly	564	9					
1957	Asian	200 CCA Mono	1,869	62	3 32	1,665	126	7 61	2 3
		750 CCA Mono	1,665	29	1 74				4 4
1957	Asian	200 CCA Mono	1,080	43	3 98	1,444	234	16 2	4 1
		750 CCA Poly without Asian strain	1,031	95	9 21				

* By permission from *Modern Medicine*, July 1, 1958, Minneapolis, Minnesota, and Frederick M Davenport, M D

† Attack rate for controls/attack rate for vaccinees.

tion ratios, and it was most fortunate that these strains were isolated sufficiently far in advance of the epidemic to make possible the production of vaccine. Strains which became available in the spring of the year were in high production by fall when the major phase of the epidemic occurred. About 10,000,000 doses of vaccine had been released for civilian use just two weeks before the epidemic peak of mid-October, 1957.

Davenport (1958b) points out that at present four families of influenza A and two of influenza B are recognized. There is some evidence to suggest that the virus involved in the pandemic of 1890 was closely related to Asian influenza 1957–58. If this indicates that the circle of antigenic variation is closing, it is possible that polyvalent vaccines may become available and effective in preventing future epidemics. The Asian vaccines, which were monovalent and made from the specific strains which later produced the epidemic in this country, confirmed the high degree of protection that can result when strains belonging to the same antigenic family are employed in the vaccine. Watch laboratories of the World Health Organization encircle the globe and make it possible to obtain valuable epidemiologic information promptly from any place on earth.

The Influenza Commission lists various indications for which vaccination may be performed. To prevent death, vaccine should be given to those with chronic debilitating disease and to pregnant women, particularly during the last trimester when the risk is greatest; also to the very young or old where mortality is known to be high. In order to prevent disease, vaccine is most effective in children in whom the attack rate is highest, approximately from five to nine years of age. In order to prevent disruption of normal community function persons concerned with health services, public safety, and public utilities and transportation should be vaccinated. Davenport (1958b) also states that it is undeniable that the homemaker

must be protected to preserve the well-being of the family unit. When all these recommendations are put together, indications are very broad indeed and would call for an active vaccination program.

The recommended dose of vaccine for adults is 400 CCA (chicken cell agglutination) units of virus. For children 6 to 12 years, the dose may be divided and given on two occasions a week apart. Multiple intradermal doses may be given to infants and preschool children. Smadel (1958) points out that while the effectiveness of the Asian vaccine has been truly amazing it would be foolhardy to assume that the same situation might be obtained in the future. An interval of six months between the time of the first strain isolations and the beginning of the epidemic was most fortunate and allowed for production of large quantities of vaccine. However, if an epidemic should begin in our own area it is inconceivable that large quantities of vaccine could be made available quickly enough to be useful in preventing the epidemic spread of influenza Salk and associates (1952) demonstrated antibody levels which were higher and endured longer when influenza vaccine was given intramuscularly as an emulsion in light mineral oil These high levels are known to persist for years, and it is possible that by some such method of hyperimmunization future control might be possible.

Although influenza vaccines have been employed in civilian and military populations and have been shown to be effective in certain influenza epidemics, there has never been wide civilian acceptance largely due to changing types and strains which have altered their effectiveness. However, when vaccines can be processed and produced from the antigenic strains that are causing the epidemic, their use will undoubtedly become more acceptable and should serve to prevent many serious complications and deaths from influenza

Abortion rates appear to be considerably increased at times

of influenza epidemics, and this in itself would indicate a possible risk to the fetus in early pregnancy (Bland, 1919; Harris, 1919). Many studies now in progress should reveal in the near future what the risk to the fetus is at such times. If a real hazard is shown to exist, certainly immunization in this selected group of patients would be highly indicated.

Treatment

Treatment consists primarily of general measures designed to reduce fever, such as salicylate therapy, and, if necessary, codeine to ease discomfort and the general aches complained of by these patients. When evidence of complications appears, such as roentgenographic shadows which indicate pneumonia or evidence of otitis media and acute bacterial tonsillitis, antibiotics are indicated and frequently prove helpful. Home treatment is considered preferable to hospital treatment where the dangers of contact with resistant staphylococci are ever present. In general, treatment should include bed rest and warm clothing, the avoidance of drafts, a simple diet, and segregation from other individuals to whom the disease might be transmitted.

Summary

Influenza is an acute infectious *myxovirus* disease which *primarily involves the respiratory passages.* The incubation period is one to two days, and illness is characterized by an abrupt onset of chills, fever, sore throat, and general aches and pains. The course is usually of two- to four-days' duration unless bacterial complications occur It is difficult to differentiate any single case of influenza from other acute respiratory illnesses in the early stages, but groups of cases may frequently be recognized from the distinct clinical manifestations Influenza is easily recognized only when epidemics occur and in military installations. The symptomatology in seasoned per-

sonnel as well as in recruits is considered highly characteristic of epidemic influenza.

The agents causing influenza are specific viruses that exert their primary pathologic effect in damaging the epithelial cells of the respiratory tract. A characteristic mononuclear reaction in pharyngeal tissues is found early in the infection. Virus can readily be recovered from respiratory secretions during the acute phase of the illness

Three distinct and possibly four or five immunologic types of influenza viruses have been identified. Type A has been associated with the most extensive and severe outbreaks. Type B may also be associated with widespread epidemic disease although epidemics of type B are often more localized and sporadic Type C has been encountered primarily in sporadic cases or limited outbreaks of mild illness. A virus isolated in Japan from pneumonitis in infants has been considered as a type D influenza, and antibodies have been demonstrated in the general population in Japan Serologic responses to types A, B, and C are sharply type-specific with little or no evidences of cross reaction Marked variation has been observed with type A strains first recognized in 1947 and designated as A prime. Variation has also been recognized among type B strains; however, type C strains to date appear to be homogeneous

Diagnostic procedures include isolation of the virus or detection of greater concentrations (fourfold or more) of specific antibody in convalescent phase serum as compared to samples taken during the early or acute stage of illness Serologic methods are simpler and therefore used routinely, however, by this method, diagnosis is often delayed until the patient is well The technique of isolation and identification is not difficult and can be performed in most bacteriologic laboratories. Prevention of influenza is well established by means of killed-virus vaccines grown in embryonated chicken eggs

Treatment is limited to rest and attention to symptom relief as well as a careful watch for complications; when they arise, a wise choice of antibiotics should be made and administered

OTHER *MYXOVIRUS* DISEASES

Para-influenza, 1, 2, and 3 (HA Virus Infections and Croup-Associated Infections)

Two new *myxoviruses* were isolated from children with acute respiratory illnesses by means of the new hemadsorption technique originally described by Vogel and Shelakov in 1957. Chanock and associates (1958), from the laboratories of the National Institute of Allergy and Infectious Diseases, reported two new viruses *which they designated as hemadsorption* viruses, types 1 and 2 These agents are similar to influenza viruses, which are *myxoviruses,* but are clearly not influenza A, B, or C *They will be referred to as M. parainfluenzae 1, 2,* and *3.*

Throat washings from patients ill with an acute respiratory disease were incubated in monkey kidney tissue cultures for five days at which time a 0 4 per cent guinea pig red cell suspension was added and the mixture held at 4° C for 20 minutes Microscopic examination then revealed the adsorption of the red cells to the monkey kidney cells in the monolayer tissue culture. Although very little cytopathogenesis may have taken place, if virus of the hemadsorption type is present, the guinea pig red cells are adsorbed to the tissue cells This *phenomenon can also be inhibited by specific antiserum.* In their original paper Chanock and associates clearly established that these newly discovered agents were not related to the *adenoviruses* nor were they directly related to several *other* newly isolated agents from patients with acute respiratory disease. The croup-associated (CA) virus first described by Chanock (1956) did not turn out to be one of the hemadsorp-

tion agents but appears to be one of the *myxoviruses*, now known as *M. para-influenzae 2*.

Hemadsorption virus type 1 (designated *M. para-influenzae 3*) was associated with acute febrile illnesses during an outbreak of respiratory disease in a nursery. The extent to which this virus produces widespread disease is not known, but Chanock and associates reported on throat swabs taken from 168 children with acute febrile respiratory illnesses and 82 control children without disease. Type 1 virus was isolated from eight of those with illness described as acute pharyngitis, bronchiolitis, or pneumonia, and from none of the 82 controls without respiratory disease. Type 1 *adenovirus* was also isolated from one child at the onset of an acute respiratory illness on November 18 and from three children under similar circumstances on November 21 and 22, and from 23 persons on November 25 and 27. The investigators thus were able to isolate virus from demonstrated infections in 27 of 54 children or 50 per cent.

In the middle of the last epidemic on November 26 throat swabs were collected from all 54 children From 18, type 1 virus was isolated Of the 26 not having illnesses, five isolations of type 1 were obtained, thus indicating a significant association of the virus with acute illness Eight of these children were studied in detail and virus was isolated from seven of them Acute and convalescent sera were available from six patients, all showed significant antibody rises by the complement-fixation test There were slight temperature elevations for approximately a three-day period. Nine patients were described as having a cough, six with medium to fine rales, and three had coarse breath sounds and rhonchi, with three instances of otitis media Rhinorrhea was prevalent and was found in 13 of the patients studied The illnesses associated with type 1 hemadsorption virus were characterized as mild in spite of the fever and associated pulmonary findings

lasted for two to three days. Type 2 virus was again recovered from eight of the individuals. The authors conclude that type 2 virus can cause respiratory illness in adults as well as the previously established illness in small children. Although the illnesses were mild, their mildness may have been related to the fact that many of the volunteers had previous antibody and also due to the fact that a small challenge dose was employed. It seems possible that this agent will now have to be assigned a more prominent place in the differential diagnosis of common respiratory disease in both adults and in children. It is apparent from the human volunteer study that the attack rate was high even in individuals who had evidence of a previous experience with the virus.

Another striking feature of this volunteer study is the cold-like symptomatology characterized by rhinorrhea, low-grade fever, and few complaints of sore throat. It would appear at this time that this agent is as close to a "common cold" virus as any that has yet been revealed and certainly probably represents *one* of the agents responsible for man's colds.

Para-influenza 2 Infection (Croup-Associated Virus)

The report by Chanock in 1956 of a *myxovirus* isolated from infants with croup appears to be unrelated to either type 1 or 2 hemadsorption agent, *adenovirus*, or to any of the influenza viruses with which we are acquainted. The agent isolated was clinically associated with croup and was therefore named croup-associated (CA) virus. It appears to possess all the properties required for classification in the *myxovirus* group, and is now designated para-influenza 2 infection.

Myxovirus multiformis, which may infect man mildly, deserves brief mention as it is closely related to influenza virus and may cross-neutralize with mumps virus. Newcastle disease virus causes conjunctivitis, for the most part in individuals who work with infected birds; recovery is complete.

Diagnosis may be confirmed by complement-fixation or by hemagglutination-inhibition tests similar to those described for influenza. *Myxovirus pestis gallis* causes fowl plague in many species of birds, and has been adapted to produce fatal infection in various mammals. *Myxovirus parotitidis* causes various forms of mumps, parotitis, meningoencephalitis, orchitis, pancreatitis, and other complications in man.

OTHER RESPIRATORY VIRUSES

Respiratory Syncytial (RS) Virus

A new virus was discovered by Morris, Blount, and Savage (1956) as a result of a spontaneous respiratory infection in a colony of chimpanzees. The new agent was designated as chimpanzee coryza agent (CCA). When grown in tissue culture the virus was capable of infecting susceptible chimpanzees. The first recovery from humans was made by Chanock, Roizman, and Myers (1957), who were successful in isolating an agent from infants with croup and pneumonia which proved to be indistinguishable from the CCA virus of chimpanzees. The cytopathic effect produced by this agent in human liver and KB cell cultures was a typical syncytium formation which accounts for the present name of respiratory syncytial virus. Chanock and Feinberg (1957), by means of serologic tests, were able to incriminate infection by this virus in 9 of 13 children with pneumonia. Further, Morris and coworkers (1956) have obtained similar evidence by showing that 13 per cent of noninfluenzal, nonadenoviral infections reacted with a positive titer against the respiratory syncytial virus.

J. H. Virus

In 1956, Price isolated 20 strains of J. H. virus from both adults and children who were suffering from coryzal illnesses

with mild sore throat and low-grade fevers. The isolation was accomplished in monkey kidney tissues in which passage was required before cytopathic effects occurred. Patients from whom washings were taken for original isolations showed titer rises in the convalescent serum, establishing the relationship of the illness to the isolate. A vaccine was prepared from monkey kidney cultures of J. H. virus which was successful in preventing illness when individuals were challenged by the virus Price reported 27 common cold-like illnesses in a group of 50 vaccinated and 50 unvaccinated children. Twenty-three illnesses occurred among the controls and only 3 in the vaccinated group. Subsequent serologic studies revealed that 20 of the 26 children had fourfold or greater antibody rises in their serum. The extent of J. H virus is not as yet known, and the significance of these studies will depend on further clinical and epidemiologic investigations. Nonetheless, a very important contribution has undoubtedly been made.

2060 Virus

This respiratory virus was also recovered from persons with mild respiratory illnesses and was first reported by Pelon and associates (1957). Original isolations were made from nasopharyngeal washings from naval recruits with mild respiratory illnesses Washings were inoculated in monkey kidney cultures, and following passage produced typical cytopathic effects Neutralizing antibodies were found in patients recovering from the illness produced by 2060 virus, and serologic surveys showed an increasing incidence in antibodies associated with increasing age. Illness was described as coryzal with mild sore throat, cough, and low-grade fever lasting three to five days Successful complement-fixing and hemagglutinating antigens have not as yet been produced from J H or 2060 viruses.

The Coe Virus

Four strains of an apparently new virus were recovered from patients with mild pharyngitis or "common cold" by Lennette and co-workers (1958). By means of various immunologic tests, the Coe virus was determined to be a newly recognized agent; the herpes simplex, *adenovirus*, Coxsackie group A (types 1–19) and group B (types 1–5), ECHO viruses (types 1–19), *myxoviruses*, RS viruses, HA agents, 2060 and J. H. viruses all failed to be neutralized. Thus another virus may be added to the growing list of viral agents responsible etiologically for acute respiratory illnesses.

Primary Atypical Pneumonia (PAP) Virus

The successful isolation of an agent from primary atypical pneumonia was first made in 1944 by Eaton, Meiklejohn, and van Herick. A paper by Liu (1957) reported eight agents from patients with primary atypical pneumonia which he was successful in identifying by indirect fluorescein-labeled antibody. The agents which he isolated were found to be antigenically related to the PAP virus originally isolated by Eaton and associates (1944) as the cause of primary atypical pneumonia. Patients with primary atypical pneumonia demonstrate a high percentage of cold hemagglutinins as well as streptococcal MG agglutinins in their serum, distinguishing this pneumonia (PAP) from that found in association with *adenovirus* infections and other forms of atypical or viral pneumonia These pneumonias are discussed in greater detail in Chapter Nine

REFERENCES

Adams, J M, *et al* (1944) An epidemic of influenza A in infants and children, *J A M.A* , 125 473.

Adams, J. M, et al. (1946): Pathologic study of the acutely inflamed human pharynx in influenza A infection, *Am. J. Dis Child.*, 71:162.

Andrewes, C. H.; Bang, F. B.; and Burnet, F. M. (1955): A short description of the *myxovirus* group (influenza and related viruses), *Virology*, 1:176.

Andrewes, C. H.; Bang, F. B; Chanock, R. M.; and Zhdanov, V. M. (1959): Para-influenza viruses 1, 2, and 3: Suggested names for recently described myxoviruses, *Virology*, 8.129

Bland, P. B (1919): Influenza in relation to pregnancy and labor, *Am. J. Obst.*, 79:184.

Bloomfield, A, and Harrop, G. A., Jr. (1919)· Clinical observations on epidemic influenza, *Bull. Johns Hopkins Hosp*, 30 1.

Chanock, R. M (1956). Association of a new type of cytopathogenic myxovirus with infantile croup, *J. Exper. Med*, 104·555.

Chanock, R. M., and Feinberg, L. (1957): Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA) II. Epidemiologic aspects of infection in infants and young children, *Am. J. Hyg*, 66 291

Chanock, R. M; Parrott, R. H; Cook, K; Andrews, B E; Bell, J A.; Reichelderfer, T.; Kapikian, A Z; Mastrota, F M; and Huebner, R J (1958): Newly recognized myxoviruses from children with respiratory disease, *New England J. Med*, 104 555.

Chanock, R. M., Roizman, B, and Myers, R (1957). Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I Isolation, properties and characterization, *Am J. Hyg.*, 66 281

Davenport, F M (1958a): Role of the Commission on Influenza, studies of epidemiology and prevention, *Pub Health Rep*, 73 133

Davenport, F. M (1958b) Recent advances in prevention of influenza by vaccination, *Mod Med*, 26 115

Dubowitz, V (1958). Influenzal encephalitis, *Lancet*, 1 140

Dunbar, J M, Jamieson, W M, Langsland, J. H M, and Smith, G H (1958) Encephalitis and influenza, *Brit M. J.*, 1.913.

Eaton, M D, Meiklejohn, G, and van Herick, W (1944)·

Studies on etiology of primary atypical pneumonia; filterable agent transmissible to cotton rats, hamsters, and chick embryos, *J. Exper. Med.*, **79**.649.

Flewett, T. H, and Hoult, J. G. (1958): Influenzal encephalopathy and postinfluenzal encephalitis, *Lancet*, **2**:11.

Francis, T, Jr. (1941): *The Significance of Nasal Factors in Epidemic Influenza in Problems and Trends in Virus Research*. University of Pennsylvania Press, Philadelphia.

Francis, T., Jr, and Stuart-Harris, C. H. (1938). Studies on the nasal histology of epidemic influenza virus infection in the ferret. I. The development and repair of the nasal lesion, *J. Exper. Med.*, **68**:789.

Gundelfinger, B. F; Stille, W. T.; and Bell, J. A. (1958)· Effectiveness of influenza vaccines during an epidemic of Asian influenza, *New England J Med.*, **259**·1005

Hamre, D; Appel, J.; and Looslı, C. G. (1956): Viremia in mice with pulmonary influenza A virus infections, *J. Lab & Clin Med.*, **47**.182.

Harris, J. W. (1919): Influenza in pregnant women, *J A M.A*, **72**·978.

Herrmann, R. E., Ogura, G. I; Johnson, E S, Toll, H W., Jr, and White, W. C. (1958): Respiratory deaths associated with Asian influenza epidemic, *J.A M.A.*, **166** 467

Hirsch, A. (1883)· *Handbook of Geographical and Historical Pathology. I. Acute Infective Diseases.* Translated by Charles Creighton, New Syndenham Society, London

Hirst, G K (1942). The quantitative determination of influenza virus and antibodies by means of red cell agglutination, *J Exper. Med*, **75** 49

Horsfall, F. L (1952)· Primary atypical pneumonia In Rivers, T M, ed, *Viral and Rickettsial Infection of Man*, 2nd ed J B Lippincott, Philadelphia, p 383

Huebner, R J (1958) Illnesses due to adenoviruses, *Mod Med*, **26**.103

Huebner, R J, Rowe, W P, and Chanock, R M (1958) Newly recognized respiratory tract viruses, *Ann Rev Microbiol*, **12** 49

Jensen, K. E., and Hogan, R. B (1958): *Laboratory diagnosis of Asian influenza*, *Pub. Health Rep*, **73**:140

Johnson, R. (1793) Inaugural Dissertation for the Degree of Doctor of Medicine, University of Pennsylvania, Philadelphia.

Kaji, M; Oseasohn, R.; Jordan, W. S, Jr; and Dingle, J H. (1959): Isolation of Asian virus from extrapulmonary tissues in fatal human influenza, *Proc. Soc. Exper. Biol. & Med.*, **100**.272.

Leichtenstern, O. (1896)· Influenza and dengue: In Nothnagel's *Specielle Pathologie u. Therapie* Alfred Holder, Wien. Bd 4, Hft. 1, pp. 1–222.

Lennette, E. H.; Fox, V. L, Schmidt, N J.; and Culver, J. O. (1958): The Coe virus, an apparently new virus recovered from patients with mild respiratory disease, *Am. J. Hyg.*, **68**:272.

Lewis, P. A, and Shope, R. E. (1931): Swine influenza II A hemophilic bacillus from the respiratory tract of infected swine, *J. Exper. Med*, **54**.361.

Liu, C. (1957)· Studies on primary atypical pneumonia I Localization, isolation, and cultivation of a virus in chick embryos, *J Exper Med.*, **106** 455.

Loosli, C G, Hamre, D; and Warner, O (1958): Epidemic Asian A influenza in naval recruits, *Proc Soc. Exper Biol. & Med*, **98** 589

MacCallum, W G (1940), *A Textbook of Pathology*, 7th ed W. B Saunders Co, Philadelphia.

McCordock, H A, and Muckenfuss, R S (1933) The similarity of virus pneumonia in animals to epidemic influenza and interstitial bronchopneumonia in man, *Am J Path*, **9** 221

McIntosh, J., and Selbie, F R (1937) The pathogenicity to animals of viruses isolated from cases of human influenza, *Brit J. Exper Path*, **18**.334

Mogabgab, W. J, and Pelon, W (1957) Problems in characterizing and identifying an apparently new virus found in association with mild respiratory disease in recruits, *Ann New York Acad Sc*, **67**:403

Morris, J. A ; Blount, R. E , Jr ; and Savage, R E (1956) Recovery of cytopathogenic agent from chimpanzees with coryza *Proc. Soc Exper. Biol. & Med*, **92**:544.

Nelson, A. A , and Oliphant, J. W. (1939) Histopathological changes in mice inoculated with influenza virus *Pub Health Rep.*, **54**:2044.

Oseasohn, R ; Adelson, L ; and Kaji, M. (1959) Clinicopathologic study of thirty-three fatal cases of Asian influenza *New England J. Med.*, **260** 509

Pelon, W ; Mogabgab, W. J.; Phillips, I A , and Pierce, W , (1957): Cytopathogenic agent isolated from naval recruits with mild respiratory illness, *Proc. Soc. Exper Biol & Med* **94**·262

Pfeiffer, R. (1893): Vorlaufige mittheilungen uber die erreger der influenza, *Deutsche med. Wchnschr.* **18**.28, *ibid* (1892) Die aetiologie der influenza, *Ztschr. Hyg.*, **13** 357

Philipson, L., and Wesslen, T. (1958): Recovery of a cytopathogenic agent from patients with non-diphtheritic croup and from day-nursery children. I. Properties of the agent *Arch ges Virusforsch.*, **8**:76.

Pierce, C. H , and Hirsch, J. G (1958). Ciliocytophthoria Relationship to viral respiratory infections of humans, *Proc Soc Exper. Biol. & Med*, **98**:489.

Podosin, R. L., and Felton, W. L (1958) II The clinical picture of Far East influenza occurring at the Fourth National Boy Scout Jamboree, *New England J Med*, **258**·778

Price, W. H (1956). Isolation of new virus associated with respiratory clinical disease in humans, *Proc Nat Acad Sc*, **42** 892

Reichelderfer, T. E , Chanock, R M , Craighead, J E , Huebner, R J ; Turner, H. C.; James, W.; and Ward, T G (1958) Infection of human volunteers with type 2 hemadsorption virus, *Science*, **128**.779

Rivers, T. M (1928) Some general aspects of pathological conditions caused by filterable viruses, *Am J Path*, **4** 91.

Salk, J E ; Bailey, M L.; and Laurent, A M. (1952). Use of

adjuvants in studies on influenza immunization, *Am. J. Hyg.*, 55:439.

Shope, R E. (1931): Swine influenza. III. Filtration experiments and etiology, *J. Exper. Med*, 54:373.

Shope, R. E. (1936): The incidence of neutralizing antibodies for swine influenza virus in the sera of human beings of different ages, *J. Exper. Med.*, 63:669.

Shope, R. E. (1958): Influenza, history, epidemiology and speculation, *Pub. Health Rep*, 73:165.

Smadel, J E. (1958): Influenza vaccine, *Pub. Health Rep*, 73: 129.

Smith, W; Andrewes, C. H.; and Laidlaw, P. P. (1933): A virus obtained from influenza patients, *Lancet*, 225.66

Steiner, P E, and Loosli, C. G. (1950): The effect of human influenza virus (type A) on the incidence of lung tumors in mice, *Cancer Res.*, 10.385.

Straub, M (1937): The microscopic changes in the lungs of mice infected with influenza virus, *J. Path & Bact*, 45.75.

Vaughn, W. T. (1921): Influenza, an epidemiologic study, *Am. J Hyg.*, Monograph Series No 1

Vogel, J, and Shelokov, A (1957). Adsorption—Hemagglutination test for influenza virus in monkey kidney tissue culture, *Science*, 126 358

Chapter Four

THE ADENOVIRUS DISEASES

INTRODUCTION

Although the first *adenoviruses* were reported by Rowe, uebner, Gilmore, Parrott, and Ward in 1953, in the next five ars more than a 150 reports of this family of viruses apared in the medical literature There are more than 20 stinct human types of adenoviruses which have been characrized; for some unexplained reason types 1 through 10 have en most frequently observed in relation to disease and are ow considered responsible for several clinical entities The riginal discovery of these agents occurred as a result of atmpts to grow adenoids and tonsils removed at operation in ssue culture preparations in the hope that such cultures might rovide suitable media for respiratory virus isolation. Cells ere found to grow out from the original fragments and after –28 days pathologic changes began to take place in the pithelial cells, which became rounded up and formed clumps his destructive process is called cytopathogenesis The preımably infected fluids were passed through fresh cultures of denoids into human embryonic tissues and also into strains f human cancer cells known as HeLa cells. A similar type of egeneration and destruction occurred in these tissues, and a istinctive type of cytopathology was recognized.

Almost simultaneously, Hilleman and Werner (1954), working in another laboratory, isolated an agent from new recruits at Ft. Leonard Wood who were ill with acute respiratory disease (ARD). This agent was originally named RI67 (respiratory infection) and was definitely shown to be etiologically responsible for the illnesses of the patients. Epidemic acute respiratory disease of military recruits called ARD was originally described by the Respiratory Commission as a "nonbacterial pharyngitis." During World War II this disease was differentiated from other respiratory illnesses such as those due to the influenza viruses and it was also shown to be distinct from the "common cold" type of illness. Acute and convalescent sera from the original cases were preserved and tested against the RI67 agent (now *adenovirus*, type 4), thus establishing the etiology of ARD.

EPIDEMIOLOGY

The *adenoviruses* are widespread in human populations and produce illness in all age groups. They have been reported from many countries of the world, including all parts of the United States, Canada, England, Holland, Sweden, Russia, and complement-fixing antibodies have been found in the sera of Egyptian children. Intensive studies in the Washington, D.C., area have shown neutralizing antibodies to be prevalent in many different age groups. Newborn infants have demonstrable complement-fixing and neutralizing antibodies comparable to those of their mothers. Studies in the Cleveland Family Group (Jordan *et al.*, 1956) indicate that most detectable antibodies are gone by six weeks of age and then are gradually acquired during the next preschool years by a very high percentage of children. More than half of the children tested between the ages of 6 and 12 months demonstrated neutralizing antibodies to at least one of the *adenoviruses*, usually type 1 or 2. The incidence gradually increases with age, and nearly

all adults have some antibody to at least one type. Seventy-two per cent had antibodies to four or more of the six types tested.

In the Cleveland Family Studies (Jordan *et al*, 1956) selected patients with acute respiratory infections were studied in order to determine the occurrence of respiratory disease caused by adenoviruses. Eighteen per cent of the selected cases showed increases in titer of neutralizing antibody for one or more of the types 1 to 7. They gathered evidence that suggested that types 2 and 5 and also possibly 1 and 3 could produce nonbacterial pharyngitis. The commonest antibodies found were against types 1, 2, and 3, which occurred in 35 to 50 per cent of adults and children Antibodies against types 4, 5, 6, and 7 were less prevalent, and they were unable to find any evidence of antibodies against type 4 in children under 18 years of age.

Jordan and associates (1957) concluded from their family studies in Cleveland that although certain of the *adenoviruses* are highly significant as causes of ARD in military recruits and certain others are etiologically related to epidemic and sporadic cases of nonbacterial pharyngitis, as a group these agents account for but a small fraction of the respiratory illnesses experienced in the civilian population They were able to isolate only 10 *adenoviruses* from 531 pharyngeal swabs collected from individuals with respiratory illnesses. Serum specimens from these same patients during the same period revealed only 1–5 per cent with significant increases in titer to types 1 to 7. Evans (1958) has recorded a similar experience with health service students in Wisconsin suffering from acute respiratory disease In his original report from the University of Wisconsin he found an average of 161 acute respiratory illnesses per 1000 students in a six-year period Respiratory infections were the single most important cause of admission to the infirmary accounting for a third of all admis-

sions. January, February, and March were the months of highest incidence, and nonbacterial respiratory infections outnumbered the bacterial illnesses by five to one.

In an intensive study of 290 students admitted for acute respiratory disease, Evans (1957) was able to establish an etiologic diagnosis of *adenovirus* infection in about 2 per cent. He concluded that a diagnosis of *adenovirus* infection could not be made on clinical grounds. Types 1, 3, and 4 were isolated in his study.

Human volunteer studies incriminated types 3 and 4 *adenoviruses* as producing clinically recognizable disease in susceptible volunteers Huebner and associates (1955) produced pharyngoconjunctival fever in volunteers who were known to have no pre-existing antibodies Hilleman, Werner, and Stewart (1955) pointed out that the viruses of the original RI family, which include some or all of the *adenoviruses*, may be responsible for undifferentiated acute respiratory disease, nonstreptococcal exudative pharyngitis, primary atypical pneumonia unassociated with cold agglutinins, pharyngoconjunctival fever, mesenteric lymphadenitis, and inapparent infections.

It now seems to be well established that the *adenovirus* infections represent one of the major causes of respiratory disease in military recruits. Hilleman and associates (1955) pointed out the immunologic heterogeneity of the agents found in military recruits, types 3, 4, and 7 being recovered repeatedly from recruits with acute respiratory illnesses including primary atypical pneumonia Rowe and Huebner (1956) state that the etiology of many, if not the majority, of undifferentiated respiratory illnesses in special military populations still remains undetermined

Studies by Loosli, Tipton, Warner, Smith, Johnston, and Hamre (1958) have further confirmed that *adenovirus* infections are a major cause of acute respiratory disease in military

inductees. They found 80 per cent of admissions from nonstudied companies, admitted to the dispensary March to May, were due to either type 3, 4, or 7 *adenovirus*. During this same period only 15 per cent of admissions from vaccinated groups were due to *adenoviruses*. The vaccine which they used appeared to be effective against all three types However, of 16 *adenoviruses* isolated after the second week from the vaccinated individuals, 15 were type 4. Antibody rises of significance occurred in only one-third of the vaccinated individuals.

During 1954, localized outbreaks in the Washington, D.C, area were studied, and infections were found to spread readily to large portions of susceptibles in households, in summer day camps, and on hospital floors In the epidemic which Parrott (1957) described, swimming pools were suspected of contributing to the spread of infection. Although the attack rate appeared to be highest in school-age children in the summer months, many infections occurred in preschool children as well as adults Retrospective serologic studies indicated that type 3 *adenovirus* was the cause of the epidemic in 1951, designated as "Greeley disease" by Cockburn and associates (1956).

LABORATORY FEATURES

Originally there was considerable confusion with the terminology as the adenoid-degenerating (AD) agent was revealed to be associated with inflammations of the adenoid, pharyngeal, and conjunctival tissues. These agents were next designated as APC viruses Hilleman's RI family group was also shown to be identical with the original isolations. A group of virologists headed by Enders (1956) decided that these agents should be called *adenoviruses*, and certain characteristics were attributed to them All types grow only in tissue cultures of certain human and simian cells and produce characteristic cytopathology in these cultures. They are nonpathogenic

for the usual laboratory animals, are heat-labile and filterable, and are resistant to antibiotics and ether. One striking and important characteristic is that they have group-specific but not type-specific soluble complement-fixing antigens. Laboratory diagnosis of the group by complement-fixation is comparatively easy, but the diagnosis of specific types is still a tedious laboratory procedure.

The size of the adenovirus particles in culture fluids has been determined to be from 80 to 120 mμ in diameter. Intracellular virus, which presents a crystalline-like pattern in the nuclei of HeLa cells, measures 65 mμ in diameter (see Fig. 9). Filtration studies indicate that the soluble antigen is not larger than 26–40 mμ.

Certain strains of *adenovirus* have been isolated from monkeys and have been designated as simian strains. Complement-fixing antibodies have been found in the serum of normal chimpanzees and guinea pigs, but none of these strains, to the writer's knowledge, has been isolated from human sources, or vice versa.

The *adenovirus* infections result in a catarrhal inflammation of the mucous membranes of the respiratory and ocular systems accompanied by a follicular enlargement of submucous and regional lymphoid tissues. They have been isolated from the intestinal tract and found in mesenteric lymph nodes, but the clinical picture which they present in the intestinal tract is not clearly defined as yet.



CLINICAL FEATURES

Adenovirus, type 3, is the cause of a clinical entity designated as pharyngoconjunctival fever. Parrott (1957) states that the chief features of this disease are follicular conjunctivitis, pharyngitis, and fever. These characteristics may occur singly as well as in combination; in the epidemic which Parrott reported asymptomatic infections were found to be rare Fever was high even in the adult patients, persisting up to four or five days A complaint of sore throat appeared to be greater than the observable pharyngitis which was recorded as having an incidence of 75 per cent in Parrott's (1957) series. Conjunctivitis also appeared in 75 per cent of the patients and was manifested by inflammation of both the bulbar and palpebral conjunctiva. No subsequent corneal lesions developed in the Washington outbreak, but corneal opacities were found as sequelae in the cases described by Cockburn and associates (1956).

Pharyngoconjunctival Fever (PCF)

An epidemic of pharyngoconjunctival fever, proved to be due to *adenovirus* type 3, occurred in a children's camp during the summer of 1955 and was reported in detail by Sobel and co-workers (1956). The clinical picture during the first wave of illness in July was characterized by a very mild pharyngitis. The patients complained of sore throat, and a fine pin-point follicular tonsillitis was found on physical examination Fevers were mild, ranging from 37 8° to 38 3 C and lasted about two days During the first wave no clear-cut diagnosis was made, however, the following significant statement appeared in the article, "Our main concern was whether the first wave represented poliomyelitis" The second wave of illness began late in July and was characterized by an illness of greater intensity, involving 62 per cent of the campers Clinical fea-

tures of this epidemic were outlined as follows: major complaints were sore throat, headache, myalgia, eye discomfort, and abdominal symptoms. Other frequent complaints included moderate stiffness and pain of neck, back, and leg muscles, suggesting a diagnosis of encephalitis or poliomyelitis.

Conjunctivitis occurred in 80 per cent of the patients, usually without any discharge. Occasionally the conjunctivitis was unilateral and lasted a few days to two weeks. The nose became obstructed during the course of the illness, and a purulent discharge developed in some patients but no severe sinusitis occurred. The tongue developed minor or marked hypertrophy of the papillae as the illness progressed. The anterior pillars of the tonsils and soft palate became involved with pin-point, coarsely granular follicles. The tonsils were moderately injected with occasional patches of whitish exudate. The eardrums were injected in one-third of the patients, and cervical adenitis was a common finding. Cough was present in only one of 130 patients. Abdominal symptoms occurred in 22 per cent of the patients, and hepatomegaly and splenomegaly were present in 18 and 12 per cent, respectively. Neuromuscular findings also occurred in 18 per cent of the patients. Fever persisted for an average of four and a half days at a level of 39.4° to 40° C. Antibiotics were used generously with no apparent effect. Bacteriologic studies were negative, but virologic studies revealed the true cause as *adenovirus* type 3, which was isolated from the conjunctiva, throat, and stool specimens in 8 of 10 subjects. The isolated agent was readily neutralized by the convalescent sera of several of the patients.

A detailed description of this new epidemic disease, now clearly described by many different authors, is presented to illustrate several of the main points which concern us vitally in this book. This epidemic illness might have been confused with any number of acute respiratory illnesses, including influenza, Coxsackie virus infections, streptococcal pharyngitis,

as primary pharyngitis, febrile common colds, tonsillitis, and upper respiratory infections. Type 4 *adenovirus* was isolated from most of the cases of nonstreptococcal pharyngitis and febrile common colds. Type 7 *adenovirus* was found predominantly in cases of tonsillitis; it was also found frequently in nonstreptococcal pharyngitis, febrile common colds, and less frequently in primary atypical pneumonia and in bronchitis.

The study reported by Berge and associates (1955) of the clinical laboratory findings of 45 hospitalized recruits with *adenovirus*, types 4 and 7, indicates that 54 per cent had exudate on the tonsils by the fourth day Cervical lymphadenopathy occurred in 40 per cent and conjunctivitis in 51 per cent, obstructive rhinitis in 76 per cent, pharyngitis in 38 per cent, cough in 93 per cent, tracheal bronchitis in 67 per cent, pneumonia in 16 per cent, and abdominal pain in 34 per cent. This symptom picture (except for cough) is strikingly similar to that described for pharyngoconjunctival fever as due most commonly to type 3 *adenovirus* Most of the clinical features of *adenovirus* infections have been considered grippe-like As far as can be ascertained from clinical detail, it is possible that influenza viruses are responsible for some of the illnesses which have been included under the term ARD

Keratoconjunctivitis

The classic form of epidemic keratoconjunctivitis (EKC) occurs most frequently in individuals ... have had eye trauma due to foreign bodies and eti... is related to *adenovirus* type 8. ... was first ... Jawetz and associates (1956) ... with ... ctivitis who were similar in a... to the ... shipyard epidemic disease ... ring Worl... is common in Jap... othe... ut rare in the United ... occas...

been observed in defense industries, particularly in workers exposed to frequent corneal trauma caused by foreign bodies and arc-welding equipment Small outbreaks have been traced to ophthalmologic clinics where tonometers and certain eye solutions were incriminated as vehicles of spread. Like follicular conjunctivitis, the infection rarely produces systemic effects but may cause prolonged conjunctivitis and keratitis The keratitic lesions show involvement of subepithelial tissues and are grossly visible. Rarely keratitis may result in permanent corneal opacities

The problem of differential diagnosis among the different *adenoviruses* is certainly most difficult. As Huebner (1958) points out, many of these illnesses, particularly as observed in infants and young children, are not characterized by localizing signs, and except for keratoconjunctivitis, each of the more specific illnesses shown in Table 3 is known to be caused by more than one type of *adenovirus*. Some *adenoviruses*, particularly types 3 and 7a, occur in several clinically separable entities

Huebner (1958) indicates that, with the exception of EKC and pharyngoconjunctival fever in acute epidemics, the symptomatology of *adenovirus* infections does not permit a clinical diagnosis. Serum antibody rises which may be demonstrated by complement-fixation or tissue culture neutralization tests show whether an adenovirus infection may have occurred in any particular patient. However, in order to establish a specific infecting serotype, the virus must be isolated in tissue culture and typed. The virus can be readily isolated in tissue culture from throat secretions and in cases with conjunctivitis from conjunctival secretions Like *enteroviruses*, *polioviruses*, and ECHO and Coxsackie viruses, *adenoviruses* are resistant to inactivation and are frequently found in the stool Caution must be exercised in the interpretation of the finding, and proof of infection established by serum antibody rises

PREVENTION

An *adenovirus* vaccine prepared in monkey kidney tissue cultures has been found useful in preventing acute respiratory

Table 3 *

CLINICAL SYNDROMES DUE TO ADENOVIRUSES

Disease	Type: Most Common	Type: Less Common	
Acute febrile pharyngitis	1, 2, 3, 5		High endemic rates of types 1, 2, and 5 in infants, type 3, epidemic, more common during cold months, similar to PCF but without conjunctivitis
Pharyngoconjunctival fever (PCF)	3, 7a, 14	1, 2, 5, 6	Epidemic in children, sporadic in adults, summer epidemics frequently associated with swimming
Acute respiratory disease (ARD)	4, 7	3, 14	Epidemic in military recruits, sporadic in civilian adults, types 4 and 7 infections rare in children
Virus pneumonia			
In infants	7a	1, 3	Rare, occurs in hospital nurseries may be fatal, similar to Goodpasture's inclusion body pneumonitis
In adults	4, 7	3	Associated chiefly with ARD, cold agglutinins not developed
Acute follicular conjunctivitis	3, 7a	2, 6, 9, 10	Sporadic adults chiefly affected
Epidemic keratoconjunctivitis (EKC)	8 (classic cases)	3, 7a (mild cases)	Epidemic adults chiefly affected, common in Japan rare in United States

* By permission from *Modern Medicine* July 1, 1958, Minneapolis, Minnesota, and R J Huebner

disease in military recruits Huebner and co-workers (1955) reported on vaccines made from type 3 in adult volunteers. They stated that among 45 volunteers injected, 35 subsequently exhibited antibodies to type 3 When challenged by the virus, 10 of the 35 individuals with antibodies developed illnesses similar to the illnesses that all 10 of the individuals who failed to develop antibodies exhibited Among the volunteers not vaccinated, 18 of 21 who had no antibodies developed illnesses In striking contrast, only 4 of 17 who had naturally acquired antibodies developed a typical illness

Bell and associates (1956) reported on the efficacy of trivalent *adenovirus* vaccine in naval recruits using a formalinized inactivated vaccine containing types 3, 4, and 7 commercially prepared and administered intramuscularly in single 2-ml doses to nearly 4000 naval recruits. There were no untoward local or general reactions. The vaccine induced a good antibody response to all three of the types employed in the vaccine. In an epidemic associated with type 4 *adenovirus*, a substantial reduction in the rate of occurrence of acute respiratory illnesses was observed, and it is clearly apparent that the usual interference with military training routine resulting from acute febrile illnesses may be reduced by *adenovirus* vaccines

In a report by Loosli and associates (1958) an inactivated and formalinized vaccine made from types 3, 4, and 7 was employed in the Naval Training Center in San Diego Half of the men in 39 companies were given vaccine and the remaining received placebos. Types 4 and 7 *adenovirus* infections were prevalent in the control population during a nine-week postvaccinal period The admission rate per thousand was 22 3 in the vaccinated group and 26.2 in the control, only a 15 per cent difference However, they point out that on the basis of *adenovirus* isolation the weekly admission rate was 3 4 for the vaccinated compared to 10 for the control, a difference of 66 per cent They concluded that *adenovirus* vac-

cines significantly reduced the number of *adenovirus* infections in the vaccinated group compared to the control group. In nonstudied companies *adenovirus* infection accounted for 80 per cent of dispensary admissions, whereas 40 per cent of admissions from the control group in the studied companies were due to either type 3, 4, or 7 *adenovirus* while only 15 per cent of the vaccinated groups were due to these agents Hilleman and co-workers (1957) concluded that *adenovirus*, types 3, 4, and 7, when prepared in a formalin-killed vaccine produced antibody levels as great as ordinarily occur after natural infection. They state that the vaccine was safe and caused no untoward reactions in man. A marked reduction in the incidence of adenovirus-caused disease requiring hospitalization during the second through fifth week after vaccination was clearly demonstrated During this period only one case of serologically positive *adenovirus* infection was hospitalized among 311 vaccinated recruits, in contrast to 61 cases among 313 controls in the same companies. This represented a 98 per cent reduction in the expected incidence The vaccine appears to be specific against *adenovirus* disease and also acts antigenically by recall stimulation. There have been insufficient studies in the civilian population to permit any conclusions as yet as to its value in this group of patients

DIAGNOSIS

The laboratory diagnosis of *adenovirus* infection depends chiefly on two procedures. virus isolation and the complement-fixation test Human cell cultures provide the most sensitive and convenient tissue for the recovery of most of the known types. The complement-fixation test, performed on early (acute) and late (convalescent) sera, provides a simple, quick, and specific diagnostic procedure but yields no information as to the infecting serotype Rowe and Huebner (1956) recommend that in order to detect all complement-fixing anti-

body rises, several antigens should be used. A neutralizing antibody rise is indicative of infection and tends to be specific for the infecting serotype, but because of the large numbers of types the procedure is of limited value for diagnostic purposes.

Chany and associates (1958) reported on severe and fatal pneumonia in infants and children associated with *adenovirus* infections. An epidemic which occurred in Hôpital St. Vincent de Paul in Paris was diagnosed as being due to *adenovirus* type 7a. It occurred during the winter months, and virus isolations were accomplished at the Pasteur Institute, Paris, as well as at the National Institutes of Health, Bethesda. Children were grouped according to age in open wards where they remained for a few weeks. When signs of illness developed they were admitted to a special hospital ward in a separate building. Twenty cases of pneumonia occurred in approximately 25 children who were in the ward at various times. In four patients the illness was described as very severe, being fatal for three infants under four years of age. In only one instance was infection observed in a child under six months of age. A family outbreak due to the same type organism (7a) involved in the epidemic at the Paris hospital was reported by Gerbeaux and associates (1957). Three children in the same family, aged 4½ years, 21 months, and 3½ months, became ill, the youngest having a mild illness with pneumonitis and complete recovery. The 21-month-old child had serous effusion, and the 4½-year-old child died from virus pneumonia and encephalitis.

Clinical manifestations were characterized by acute onset with cough and temperature elevations to 39° C or above. Antibiotics had no effect on the temperature curve, physical findings were consistent with pneumonitis. Conjunctivitis was also a feature, and occasionally a morbilliform eruption was observed. Autopsy findings showed a typical bronchial necrosis with intranuclear inclusion bodies similar to those reported

by Goodpasture and co-workers (1939). Type 7a *adenovirus* was isolated from the spinal fluid obtained the day before death, and from brain and lung tissue at autopsy. It would appear from the experience of the French workers that *adenovirus* infections may be fatal in young children and should be taken seriously. In special populations such as those in the Hôpital St. Vincent de Paul in Paris the authors raise the question as to whether or not *adenovirus* vaccine should be employed for protection against a severe epidemic due to an agent for which there is an effective vaccine. It would appear to be a wise choice for them

SUMMARY

There are at least 20 serologically distinct types of *adenoviruses* having a common complement-fixing antigen and similar biologic properties. Types 1, 2, 3, and 5 have been found most frequently in association with acute febrile pharyngitis in young children and can be unmasked in tissue cultures of adenoids and tonsils of most children undergoing tonsillectomy and adenoidectomy. The type 3 virus occurs in both civilian and military populations where it causes an entity described as pharyngoconjunctival fever. Types 4 and 7 cause a significant proportion of ARD and atypical pneumonia in military recruits Types 3 and 7a have been isolated frequently in association with conjunctivitis, and type 8 causes epidemic keratoconjunctivitis Virus pneumonia in infants has been shown to be due to types 7a, 1, and 3 As many as 7 different types of *adenoviruses* have been associated with pharyngoconjunctival fever, which might be considered the prototype illness due to *adenoviruses*.

·ERENCES

Bell, J A , *et al* (19 cy of trivale us (ACP) vaccine in nava *A.M.A.*, 16

Berge, T O ; England, B ; Mauris, C.; Shuey, H. E ; and Lennette, E. H (1955): Etiology of acute respiratory disease among service personnel at Fort Ord, Calif , *Am. J. Hyg* , **62**.283

Blattner, R J (1958). Comments on current literature. Adenovirus pneumonia, *J Pediat.*, **53** 631

Chany, C ; Lépine, P , Lelong, M , Le-Tan-Vinh; Satgé, P.; and Virat, J (1958): Severe and fatal pneumonia in infants and young children associated with adenovirus infection, *Am. J Hyg.*, **67**·367

Cockburn, T A , Rowe, W P., and Huebner, R J. (1956)· Relationship of the 1951 Greeley, Colorado, outbreak of conjunctivitis and pharyngitis to type 3 APC virus infection, *Am J Hyg* , **63** 250

Commission on Acute Respiratory Diseases (1946). Acute respiratory disease among new recruits, *Am. J Pub Health*, **36** 439

Drouhet, V (1957) Étude d'un virus APC (adéno-virus) isc d'un cas de pneumopathie mortelle, *Ann. Inst. Pasteur*, **9**; 138

Enders, J F , *et al* (1956) "Adenoviruses" Group name pro posed for new respiratory tract viruses (report). *Science*, **124** 119

Evans, A S (1957) Acute respiratory disease in University of Wisconsin students, *New England J Med* , **256** 377

Evans, A S (1958) Adenovirus infections in children and young adults, with comments on vaccination, *New England J Med* , **259** 464

Gerbeaux, J , Heber-Jouas, J , Masse, N , and Beauchef, A (1957) Epidemie familiale de maladie à virus du groupe APC chez trois enfants (un cas mortel), etude clinique, anatomique et virologique, *Bull et mém Soc méd hôp Paris*, **73** 519

Ginsberg, H S , Badger, G F , Dingle, J H , Jordan, W S , Jr , and Katz, S (1955) Etiologic relationship of the RI-67 agent to "acute respiratory disease (ARD)," *J. Clin Invest* , **34** 820

Goodpasture, E W , Auerbach, S H , Swanson, H S , and Cotter,

E. F. (1939): Virus pneumonia of infants secondary to epidemic infections, *Am J. Dis Child*, 57:997.

Hilleman, M R. (1957): Epidemiology of adenovirus respiratory infections in military recruit populations, *Ann. New York Acad. Sc.*, 67.262.

Hilleman, M. R., and Werner, J. H. (1954): Recovery of new agent from patients with acute respiratory illness, *Proc. Soc. Exper. Biol. & Med.*, 85·183.

Hilleman, M. R ; Werner, J H.; and Stewart, M. T. (1955): Grouping and occurrence of RI (prototype RI-67) viruses, *Proc. Soc. Exper. Biol. & Med.*, 90.555

Huebner, R J (1958). Illnesses due to adenoviruses, *Mod. Med*, 26:103

Huebner, R J.; Bell, J. A.; Rowe, W. P ; Ward, T. G ; Suskind, R G ; Hartley, J W ; and Paffenbarger, R. S , Jr (1955) Studies of adenoidal-pharyngeal-conjunctival vaccines in volunteers, *J.A.M.A.*, 159.986

Jawetz, E ; Hanna, L ; Kimura, S J ; and Thygeson, P (1956) A new type of APC virus from follicular conjunctivitis, *Am J Ophth.*, 41.231

Jordan, W S , Jr (1957) The frequency of infection with adenoviruses in a family study population, *Ann. New York Acad Sc.*, 67 273

Jordan, W S , Jr , *et al* (1956) A study of illness in a group of Cleveland families. X The occurrence of adenovirus infections, *Am J Hyg*, 64 336

Loosli, C G , Tipton, V C , Warner, O , Smith M , Johnston, P B , and Hamre, D (1958) Adenovirus vaccine evaluation study in naval recruits, *Proc Soc Exper Biol & Med*, 98 583

Morgan, C , Godman, G C , Rose, H M , Howe, C , and Huang, J S (1957) Electron microscopic and histochemical studies of an unusual crystalline protein occurring in cells infected by type 5 adenovirus Preliminary observations, *J Biophys Biochem Cytol*, 3 505

Parrott, R H (1957) Newly isolated viruses in respiratory disease, *Pediatrics*, 20 1066

Rowe, W. P.; Huebner, R. J; Gilmore, L. K.; Parrott, R. H.; Ward, T. G. (1953): Isolation of cytopathogenic agents from human adenoids undergoing spontaneous degeneration in tissue culture, *Proc. Soc. Exper. Biol. & Med*, 84 570.

Rowe, W. P., and Huebner, R. J. (1956): Present knowledge of the clinical significance of the adenoidal-pharyngeal-conjunctival group of viruses, *Am J. Trop. Med*, 5 453.

Sobel, G.; Aronson, B; Aronson, S.; and Walker, D. (1956): Pharyngoconjunctival fever. report of epidemic outbreak, *Am. J. Dis. Child.*, 92.596.

E. F. (1939): Virus pneumonia of infants secondary to epidemic infections, *Am. J. Dis. Child.*, 57.997.

Hilleman, M. R. (1957): Epidemiology of adenovirus respiratory infections in military recruit populations, *Ann. New York Acad. Sc.*, 67:262.

Hilleman, M. R., and Werner, J. H. (1954): Recovery of new agent from patients with acute respiratory illness, *Proc. Soc. Exper. Biol. & Med.*, 85.183

Hilleman, M. R.; Werner, J. H; and Stewart, M. T. (1955). Grouping and occurrence of RI (prototype RI-67) viruses, *Proc. Soc Exper. Biol. & Med*, 90:555

Huebner, R J. (1958)· Illnesses due to adenoviruses, *Mod. Med*, 26:103.

Huebner, R. J.; Bell, J. A.; Rowe, W. P.; Ward, T. G.; Suskind, R G; Hartley, J W.; and Paffenbarger, R. S, Jr. (1955): Studies of adenoidal-pharyngeal-conjunctival vaccines in volunteers, *J A.M.A*, 159:986

Jawetz, E, Hanna, L; Kimura, S J., and Thygeson, P. (1956): A new type of APC virus from follicular conjunctivitis, *Am J. Ophth*, 41 231

Jordan, W. S, Jr (1957). The frequency of infection with adenoviruses in a family study population. *Ann New York Acad. Sc.*, 67 273

Jordan, W S, Jr, *et al* (1956) A study of illness in a group of Cleveland families X The occurrence of adenovirus infections, *Am J Hyg*, 64 336

Loosli C G, Tipton, V C, Warner, O, Smith, M, Johnston, P. B., and Hamre, D (1958) Adenovirus vaccine evaluation study in naval recruits, *Proc Soc Exper Biol & Med*, 98 583

Morgan, C, Godman, G C, Rose, H M., Howe, C, and Huang, J S (1957) Electron microscopic and histochemical studies of an unusual crystalline protein occurring in cells infected by type 5 adenovirus Preliminary observations, *J Biophys Biochem Cytol*, 3 505

Parrott, R H (1957) Newly isolated viruses in respiratory disease, *Pediatrics*, 20 1066

evaluate the relationship of the *enterovirus* infections in the over-all picture of respiratory disease, it will be necessary to understand and become acquainted with the entire picture of illness produced by these agents. This is a rapidly changing field, and only in the last few years have we come to appreciate the respiratory symptomatology that is frequently associated with some of these infections. It is important again that we recognize the clinical spectrum of disease in order to diagnose and treat these protean illnesses

In the case of the symptom of diarrhea, Ramos-Alvarez and Sabin (1954) raise the pertinent question of the etiologic significance of the various viruses that are being recovered from infants and children with diarrheal diseases They indicate that although *polioviruses* and cytopathogenic Coxsackie viruses were recovered with the same frequency in both groups, diarrheal and nondiarrheal, it is impossible to be sure that they were not responsible for the illness observed in the children from whom they were isolated. The reasons they give for this are as follows: (1) all of these viruses are known to produce a spectrum of clinical manifestations ranging from inapparent infections and minor illnesses to more severe disease with varying degrees of involvement of the central nervous system; (2) the diarrheal illness occurred concurrently with an acute infection, as shown by the development of neutralizing antibodies during convalescence, and (3) although some of the patients in the control groups from whom viruses were recovered may have had only inapparent infections, they point out that it is possible that others might have had some illness with or without diarrhea subsequent to the time of sampling Further details of the role of the ECHO viruses in diarrhea and the etiology of diarrhea will be presented later in the section directly concerned with these agents

Although we recognize the wide variety of symptoms that are related to the central nervous system (aseptic meningitis),

Chapter Five

THE ENTEROVIRUS DISEASES

INTRODUCTION

The Committee on Enteroviruses of the National Foundation for Infantile Paralysis determined that this family of viruses should include the Coxsackie viruses, groups A and B, the *polioviruses*, and the new ECHO (enteric cytopathogenic human orphan) viruses. In this large family there are more than 50 distinct viruses, including 3 types of *polioviruses*, 25 types of Coxsackie A, 5 types of Coxsackie B, and 25 or more types of ECHO viruses These agents are all known to be multiplying at various times in the human intestinal tract It is clear that the list is far from complete and in the near future new types will undoubtedly be added

Although all of these agents appear to be closely allied etiologically to aseptic meningitis, there is a wide variety of clinical manifestations which are now being attributed to certain of the *enteroviruses* Among the varied manifestations, evidence of acute respiratory disease has been clearly identified with certain of the agents in all three of the major groups In this chapter the Coxsackie viruses will be discussed separately as well as *poliovirus* and ECHO virus infections Emphasis will be placed on the respiratory features, but in order to

evaluate the relationship of the *enterovirus* infections in the over-all picture of respiratory disease, it will be necessary to understand and become acquainted with the entire picture of illness produced by these agents. This is a rapidly changing field, and only in the last few years have we come to appreciate the respiratory symptomatology that is frequently associated with some of these infections. It is important again that we recognize the clinical spectrum of disease in order to diagnose and treat these protean illnesses.

In the case of the symptom of diarrhea, Ramos-Alvarez and Sabin (1954) raise the pertinent question of the etiologic significance of the various viruses that are being recovered from infants and children with diarrheal diseases. They indicate that although *polioviruses* and cytopathogenic Coxsackie viruses were recovered with the same frequency in both groups, diarrheal and nondiarrheal, it is impossible to be sure that they were not responsible for the illness observed in the children from whom they were isolated. The reasons they give for this are as follows. (1) all of these viruses are known to produce a spectrum of clinical manifestations ranging from inapparent infections and minor illnesses to more severe disease with varying degrees of involvement of the central nervous system, (2) the diarrheal illness occurred concurrently with an acute infection, as shown by the development of neutralizing antibodies during convalescence; and (3) although some of the patients in the control groups from whom viruses were recovered may have had only inapparent infections, they point out that it is possible that others might have had some illness with or without diarrhea subsequent to the time of sampling. Further details of the role of the ECHO viruses in diarrhea and the etiology of diarrhea will be presented later in the section directly concerned with these agents.

Although we recognize the wide variety of symptoms that are related to the central nervous system (aseptic meningitis),

in each group certain agents have been identified with acute respiratory disease and the relationship between respiratory and gastrointestinal symptoms produced by many of these viruses is becoming clearer. The *enteroviruses* may produce disease in the central nervous system, gastrointestinal tract, and respiratory passages, and although they all cause aseptic *meningitis certain types have been predominantly associated* with gastrointestinal or respiratory symptomatology, including *the development of severe interstitial pneumonitis and death.*

THE COXSACKIE VIRUS INFECTIONS

In 1949 Dalldorf and associates first reported on an unidentified filterable agent isolated from feces of children with paralysis The original cases occurred in the town of Coxsackie, New York, in patients who appeared to be afflicted with poliomyelitis The viruses have continued to be called the Coxsackie viruses and have since been found in all parts of the world and associated with many different illnesses

Since the discovery of the Coxsackie group of viruses a great deal has been learned about them The family is a large one, now reported to have 30 distinct types which fall into two groups, A and B, and as pointed out previously are only part of a large family of *enteroviruses* The method of employing newborn mice in the study of stool specimens was responsible for the discovery of this new group of Coxsackie agents When tissue cultures were added to the methods, additional viruses were discovered, and Dalldorf points out that different techniques yield different results Any thorough survey of stool specimens must now include not only animal studies but a rather wide variety of tissue culture cells.

The Coxsackie viruses readily infect and produce disease in suckling mice but do not cause disease in adult mice They are quite similar to the *polioviruses* in their general distribution, size, and resistance to physical agents and they tend to

occur in the same seasons of the year. They may be found in both throat washings and feces of infected individuals.

Experimentally, two large groups of agents may be distinguished and separated by their distinct serologic characteristics. The group A types are commonly related to febrile illnesses in young individuals during the summer months. The illnesses are characterized by headache, with some stiffness of the neck and muscle soreness. A form of vesicular pharyngitis with small serous blisters on the pharynx is also typical of several of the agents in the group A classification. Group B types are etiologically related to epidemic pleurodynia (Bornholm disease), which clinically is characterized by sudden onset of fever and severe pain in the chest region (devil's grip) with accompanying signs of meningitis in many patients. A large epidemic of acute meningoencephalitis has been caused by Coxsackie B virus, and the virus has also been definitely associated with acute fulminating myocarditis in infants.

The presence of the Coxsackie virus is readily determined by isolation in suckling mice of the agent from stool specimens or throat washings. Further proof of infection is gained by neutralization tests with acute and convalescent samples of the patient's serum which may be tested against the isolated strain of virus. A rise in titer for the type may be diagnostic, but frequently the rise occurs too early to be of much value in diagnosis, and some healthy individuals may have an elevated titer in their blood. Simultaneous infection with other viruses, particularly *poliovirus*, or other Coxsackie agents, also leads to confusion.

The Coxsackie viruses may be readily distinguished from *polioviruses* by the susceptibility of suckling mice and the resistance of monkeys. Certain of the Coxsackie viruses can be isolated in tissue culture, which at present is of great interest inasmuch as some of these agents are neither pathogenic for monkeys nor for suckling mice. The group A Coxsackie

viruses induce flaccid paralysis and degeneration of muscles, but fail to affect the central nervous system in suckling mice. The group B agents tend to cause encephalomyelitis with focal myositis, pancreatitis, and fat necrosis in suckling mice. Figure 10 illustrates Coxsackie A10 virus particles and crystals.

Clinically a distinction can be drawn between the groups, the A types being frequently associated with vesicular pharyngitis or herpangina whereas the B agents commonly cause pleurodynia and aseptic meningitis. It is also clear that certain of the A strains are responsible for aseptic meningitis

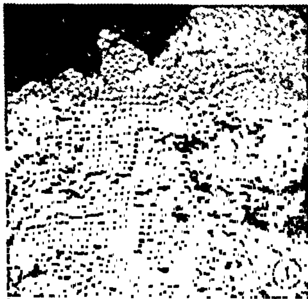
The first clinical descriptions of herpangina or vesicular pharyngitis are attributed to Zahorsky (1920), who described an acute febrile disease in children characterized by tiny vesicles on the pharynx and soft palate which later became ulcerated The association between this entity and the group A Coxsackie viruses is now well established.

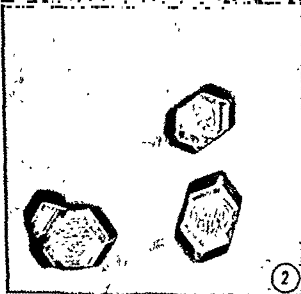
Epidemiology

The agents are known to produce disease throughout the world and occasionally almost reach pandemic proportions In 1955 and 1956 large outbreaks occurred in Minnesota and Iowa and the following year in North Carolina. In 1955 group A virus was common in Italy as well as in much of western Europe and Great Britain. An unusual epidemic produced by group A16 virus occurred in Toronto and was characterized by aseptic meningitis, ulcerative lesions in the mouth, and vesiculated skin lesions with ulcers occurring on the fingers

---

Figure 10. (1) An electron micrograph of Coxsackie virus A10, showing particles in square and hexagonal packing in different crystal planes Particle size is 27 mμ, and the magnification is approximately 60,000 ×. (2) Photomicrograph of crystals of the same virus which measure approximately 100 μ in their maximum diameter (From Mattern, C F T, and DuBuy, H G [1956] Purification and crystallization of Coxsackie virus, *Science*, 123 1037)


1


2

Coxsackie viruses have been found particularly during the summer months in surveys of stool specimens from patients with diarrhea as well as from normal subjects. It now appears from various reports throughout the world that approximately 3–5 per cent of well individuals may harbor the Coxsackie viruses. It is not clearly established whether these agents may represent inapparent infection or may be present in the stools as a result of previous illness which may have been inapparent. *Patients with group A viruses who suffer from vesicular pharyngitis* have been known to excrete virus in the stool for many days or weeks following recovery.

Coxsackie viruses are found predominantly during the summer and fall months and appear to correlate closely with the incidence of herpangina or vesicular pharyngitis. Epidemiologic studies indicate that they primarily infect children and that whole families may be involved, indicating the high infectivity of the agent with spread from person to person. The *incubation period varies widely but averages four to five days* in most of the reported series.

Clinical Features

Of the first 19 types of Coxsackie A that have been defined, types 2, 4, 5, 6, 8, and 10 have definitely been *identified with* vesicular pharyngitis. Several other reports indicate that Coxsackie A may cause acute pharyngitis without vesicular formation. Certain established isolations reveal a four-day incubation period with a clinical illness characterized by dysphasia, general aching, pharyngeal erythema, chest pains, chills, and acute pharyngitis. In a series of children reported from Washington, D.C., the onset of disease was sudden with fever associated with most of the illnesses. Although the fever tends to *be low grade, averaging 37.8° to 38.9° C, it may* rarely reach 40.6° C. The fever is usually of short duration, lasting two to four days in most patients.

In the Children's Hospital, Washington, D.C., 4 out of 68 children had associated convulsions and approximately 70 per cent of the children complained of sore throat and difficulty in swallowing Headache and abdominal pain were also prominent symptoms. However, the most outstanding manifestation of group A Coxsackie disease is the presence of characteristic gray-white papulovesicular lesions measuring about 1–2 mm in diameter. These are followed quickly by ulceration. Lesions are located on the anterior pillars and tonsillar fossae and may occur on the soft palate, uvula, and tonsils The ulcerated lesions persist for a week to two and may be confused with infectious gingivostomatitis caused by herpes simplex virus. The latter agent is known to produce febrile illness associated with vesicles and ulcers in the mouth which also occur in the pharyngeal area Herpes simplex virus tends to cause disease in any season of the year rather than in the summer months, which is also characteristic of the Coxsackie A viruses. Further differentiation is based on the location of the lesions which in the case of the herpes virus tend to be on the tongue, lips, and buccal and sublingual mucosa Rarely the vesicular ulcerating lesions may occur on the labia majora and have been definitely associated with the Coxsackie A virus

Pathologically the lesions attributed to Coxsackie group A agents are limited to their local effect on the mucous membranes There appears to be no involvement of major organs, and the occurrence of convulsions is not accompanied by pleocytosis The white blood cell response as viewed in the peripheral blood is unpredictable in the Children's Hospital series 53 per cent had counts under 10,000 per milliliter, 20 per cent ranged from 10,000 to 15,000 per milliliter, and 27 per cent were over 15,000 per milliliter It has now been shown that many of the Coxsackie A viruses are capable of causing aseptic meningitis which is difficult to separate from the group B viruses, the ECHO viruses, and *polioviruses*

viruses, which are widely distributed throughout the world, may produce disease in man without involving the central nervous system. Since the severe epidemic which occurred in Minnesota in 1946 it has been apparent to this writer that acute sore throat may be one of the chief complaints and a striking clinical manifestation of poliomyelitis. In the 1946 epidemic it was shown that acute pharyngitis occurred in a high percentage of children suffering from what was clinically diagnosed as poliomyelitis. *Grulee and Panos (1948)* pointed out that acute pharyngitis was one of the outstanding presenting signs in patients who were treated at the University of Minnesota Hospital.

As part of a study of illnesses in a group of Cleveland families, *Jordan, Stevens, Katz, and Dingle (1956) reported* the recognition of family epidemics of poliomyelitis and pleurodynia during a search for respiratory disease viruses. This paper has great significance in that it demonstrates that in four different families an acute respiratory disease was taking place *which the families called "grippe." In three of the families* viruses were isolated, and serum studies clearly indicated that *polioviruses* were involved in the family epidemics. In the fourth family a Coxsackie B 3 agent was found to be responsible for the symptomatology of respiratory disease. It is a most convincing demonstration of the fact that *poliovirus* and Coxsackie virus infections must be seriously considered in the differential diagnosis of undifferentiated respiratory disease.

The type 2 virus has been closely allied with acute respiratory disease in an epidemic reported from the Children's Clinic of Bremen by *Schall, Lennartz, and Hake (1956)*. In summary, they state that all of the children in the isolation ward of a clinic for infants became ill with a mild fever and symptoms relating to the upper respiratory passages. They identified the virus as *poliovirus* of the Lansing type in all cases examined. *They characterized the epidemic by a rapid*

spreading and mild clinical symptoms. They pointed out the difficulty in differentiating inapparent or abortive forms of Heine-Medin disease. It is apparent that an epidemic involving 26 cases occurring largely in the infant age group produced a clinical picture of respiratory disease almost exclusively. Nearly all of the patients were described clinically as having an acute rhinopharyngitis with few other complications. The febrile illnesses as recorded were low grade, and in only a few patients did the fever rise to 40° C. Neutralization tests for all three types of virus were performed, and significant rises to *poliovirus* type 2 were recorded with no positive findings for types 1 or 3.

In a recent paper Sobel and co-workers (1956), describing the details of an epidemic of *adenovirus* type 3 commonly designated as pharyngoconjunctival fever, indicated on three different occasions in their paper that the diagnosis of poliomyelitis was seriously considered. The first wave of the epidemic was characterized by mild illness with low-grade fever and mild pharyngitis. They pointed out that stiff neck and back were among the classic symptoms observed, it is no wonder that they were disturbed about poliomyelitis. The etiologic approach to the disease, however, established the fact that *adenovirus* type 3 was the causal factor and that none of the three types of *poliovirus* was involved.

Salk (1958) has indicated that the widespread use of poliomyelitis vaccines has altered the epidemiology of this disease. A re-evaluation of the epidemiologic features of poliomyelitis may be necessary, particularly in light of the large family group of *enteroviruses* which now closely simulate each other Dalldorf (1958), as pointed out previously in this chapter, indicated that there might be some interference existing between Coxsackie B and poliomyelitis viruses It seems possible that the widespread use of polio vaccine might account for the apparent increase in ECHO virus infections as

well as other forms of aseptic meningitis, particularly those due to Coxsackie viruses.

The first evidence of the virus etiology in poliomyelitis was presented as early as 1909, but only within the last 10 years have we appreciated the three immunologic types as being responsible for most of the various epidemics as well as sporadic cases of poliomyelitis Any of the previous small epidemic and sporadic cases may well have been related to Coxsackie and ECHO viruses.

Among the three types, type 1 has been the principal contributor to the paralytic form of the disease, but infection is readily produced by all three. Man undoubtedly is the primary host and principal reservoir of *polioviruses* with evidence that he also is responsible for the infectious and contagious nature of the disease. No intermediate vectors have been shown to be significant in its transmission. The relationship of bowel-excreted virus to oral-pharyngeal sources of infection is not completely settled. In communities where hygiene is such that sewage contamination is high, it is possible that this may be the primary factor in its spread. Salk (1958) indicates that in earlier times and in regions where personal hygienic practices are not of the most modern type, exposure probably occurs in infancy at a time when the baby may be under the influence of maternal antibodies, with paralysis rare and lifetime immunity resulting from infection With changing hygienic habits it is possible that pharyngeal viruses may play an important role in the spread of disease and that, as such, control of pharyngeal excretion of virus may be greatly reduced by the use of killed-virus vaccines.

It is conceivable that the spread of virus may be diminished by effective vaccination and an even greater reduction in the incidence of poliomyelitis may occur than could be attributable to the actual number of individuals vaccinated. The occurrence of secondary contact cases strongly favors the pharyngeal

route as being highly significant in the transmission of infection. The virus persists in the pharynx for a matter of days, whereas in the stool it may continue to be evident for weeks or months This problem is still unsolved.

The blood stream is considered the principal pathogenic mechanism by which *poliovirus* enters the central nervous system, and it now appears evident that antibodies in the blood will actually protect against the paralytic forms of the disease. Salk (1958) points out that a single dose of vaccine results in greater type 1 antibody response in persons who have had a prior natural type 2 infection than in patients who had prior type 3 infection. He also indicates that prior type 2 infection is less apt to be followed by paralysis when an individual is attacked by the type 1 virus Antibody production is related directly to the amount of antigen injected, and by and large the degree of persistence of these levels appears to be related to the degree of potency of the primary agent as well as the intensity of the booster doses. When a good antibody level has been induced it tends to persist.

A change in age incidence has occurred since the widespread use of vaccination with increases in the group under five years This would indicate a tendency to revert to the age group that was first recognized in the early history of poliomyelitis and from which it gained the name of infantile paralysis. Salk (1958) believes this may be due to the fact that the amount of virus in the community has been reduced as a result of vaccination programs He states that it is possible that killed-virus vaccine does in fact have some effect on the significant mode of egress of virus from the infected individual

The question of reinforcing immunity with booster inoculations will have to be settled in the future as the epidemiology of the immunized population becomes more clearly evident The killed-virus vaccines of poliomyelitis are now being employed in combination with other immunizing agents in

pediatric practice with good results. It is possible with further study of the problem that when polyvalent respiratory vaccines are considered in the future introduction of certain strains of *poliovirus* may be indicated. Although the respiratory features of this disease are limited, it is obvious that mild illness may occur which can closely simulate various respiratory diseases. In the summer months particularly when a child has an acute pharyngitis with low-grade fever and headache, the diagnosis must be differentiated from Coxsackie, ECHO, and certain of the *adenovirus* infections.

ECHO VIRUS INFECTIONS

ECHO (enteric cytopathogenic human orphan) viruses were recognized when tissue culture began to be used as a common method for the isolation of *polioviruses* in stool specimens. Just as the Coxsackie viruses were discovered when a new tool was introduced (the suckling mouse) the introduction of kidney tissue cultures revealed the naturally occurring viruses, now known as ECHO viruses, which are a part of the large family of *enteroviruses* under discussion in this chapter Some 24 or 25 distinct antigenic types are now recognized, and Sabin (1958) indicates that many are waiting to join the long list

The ECHO viruses produce a transitory infection of the alimentary tract and are considered in no way comparable to the enteric bacteria, which are lifelong residents of this area The incidence of ECHO viruses in the stools of healthy humans is most prevalent during the summer in young children and among large families of the low-economic group Certain of the 25 studied types of ECHO viruses, such as 8, 10, and 20, appear to have a predilection for the respiratory passages and may disseminate more extensively during the colder months of the year

The ECHO viruses all appear to share the following charac-

teristics: they are cytopathogenic for monkey and human cells in tissue culture; they are not neutralized by the three types of *poliovirus* antisera, nor by the antisera for the Coxsackie viruses, some of which are now known to be cytopathogenic for tissue culture; the ECHO viruses do not cause disease in infant mice as do the Coxsackie agents; they are neutralized by human gamma globulin and individual human sera. A group of infants admitted to an orphanage in Washington, D.C., was studied in detail by workers at the National Institutes of Health (Cramblett *et al.*, 1958) Among the group studied, six infants were found to have suffered a recent infection with an ECHO virus. The agent was originally referred to as JV-1 virus, and in each instance the illness appeared to be associated with mild respiratory symptoms.

According to Cramblett and associates (1958), the major manifestations were fever, coryza, mild erythema of the pharynx and eardrums, as well as abnormal stools. The fevers were moderately elevated for two days or less. Coryza, manifested by rhinorrhea, sneezing, and irritability, was present in all six infants and was the most outstanding symptom. Rhinorrhea was profuse, serous in character, and later became purulent. Cough was a striking symptom in five of the six patients, and erythema of the tonsillar fossae and pillars was also present Myringitis was evident in the eardrums, which became full, distorted, and complicated by purulent otitis media in one patient The stools of all patients were abnormal, with frank diarrhea in four and frequency persisting no longer than two days Some evidence of mild conjunctivitis was present, with crusting and discharge in a few patients. The cervical lymph nodes appeared to be enlarged in four patients.

Laboratory studies revealed white blood counts between 6000 and 15,000 per milliliter, with a predominance of lymphocytes in all of the patients except one. The sedimentation rate by the Westergren method was moderately elevated

pediatric practice with good results. It is possible with further study of the problem that when polyvalent respiratory vaccine are considered in the future introduction of certain strains of poliovirus may be indicated. Although the respiratory features of this disease are limited, it is obvious that mild illness may occur which can closely simulate various respiratory diseases. In the summer months particularly when a child has an acute pharyngitis with low-grade fever and headache, the diagnosis must be differentiated from Coxsackie, ECHO, and certain of the *adenovirus* infections.

ECHO VIRUS INFECTIONS

ECHO (enteric cytopathogenic human orphan) viruses were recognized when tissue culture began to be used as a common method for the isolation of *polioviruses* in stool specimens. Just as the Coxsackie viruses were discovered when a new tool was introduced (the suckling mouse) the introduction of kidney tissue cultures revealed the naturally occurring viruses, now known as ECHO viruses, which are a part of the large family of *enteroviruses* under discussion in this chapter. Some 24 or 25 distinct antigenic types are now recognized, and Sabin (1958) indicates that many are waiting to join the long list.

The ECHO viruses produce a transitory infection of the alimentary tract and are considered in no way comparable to the enteric bacteria, which are lifelong residents of this area. The incidence of ECHO viruses in the stools of healthy humans is most prevalent during the summer in young children and among large families of the low-economic group. Certain of the 25 studied types of ECHO viruses, such as 8, 10, and 20, appear to have a predilection for the respiratory passages and may disseminate more extensively during the colder months of the year.

The ECHO viruses all appear to share the following charac-

teristics: they are cytopathogenic for monkey and human cells in tissue culture; they are not neutralized by the three types of *poliovirus* antisera, nor by the antisera for the Coxsackie viruses, some of which are now known to be cytopathogenic for tissue culture; the ECHO viruses do not cause disease in infant mice as do the Coxsackie agents; they are neutralized by human gamma globulin and individual human sera. A group of infants admitted to an orphanage in Washington, D.C., was studied in detail by workers at the National Institutes of Health (Cramblett *et al.*, 1958). Among the group studied, six infants were found to have suffered a recent infection with an ECHO virus. The agent was originally referred to as JV-1 virus, and in each instance the illness appeared to be associated with mild respiratory symptoms.

According to Cramblett and associates (1958), the major manifestations were fever, coryza, mild erythema of the pharynx and eardrums, as well as abnormal stools. The fevers were moderately elevated for two days or less. Coryza, manifested by rhinorrhea, sneezing, and irritability, was present in all six infants and was the most outstanding symptom. Rhino-

[illegible]

[illegible] which became full, distorted, and complicated by purulent otitis media in one patient. The stools of all patients were abnormal, with frank diarrhea in four and frequency persisting no longer than two days. Some evidence of mild conjunctivitis was present, with crusting and discharge in a few patients. The cervical lymph [illegible] enlarged in four [illegible]

[illegible] between [illegible]

lymphocytes in all of the patients except one. The sedimentation rate by the Westergren method was moderately elevated

in five of the patients, and the test for C-reactive protein was positive in one patient only. Paired sera from the patients failed to demonstrate a rise in titer for antistreptolysin O, cold agglutinins, or heterophil antibodies. Four of the six patients showed abnormal chest roentgenograms with increase in bronchovascular markings, hilar lymphadenopathy, and frank pulmonary infiltration. *Intense viral studies were carried out* on this small group of patients, and material from throat swabblings was placed in HeLa cells and monkey kidney cell cultures. Rectal swabs were also inoculated into monkey kidney cell cultures.

Specimens of serum from the patients were tested simultaneously. All six patients yielded virus cytopathogenic for monkey kidney cell cultures which appeared to be different from any previously isolated agents. The cytopathic effects were similar to those produced by *polioviruses* and ECHO viruses. The agent was not pathogenic for newborn mice, and *the complement-fixing antigen was absent for the adenoviruses* Cramblett and associates were able to conclude that the JV-1 agent was apparently a newly recognized virus which satisfied the criteria for the ECHO group. Great significance must be attached to this important contribution which clearly associates an ECHO virus (type 20) with primary respiratory disease.

The spectrum of clinical illness is not the same for all ECHO viruses It is equally clear that similar clinical manifestations may be produced by a great variety of etiologic agents. Ramos-Alvarez and Sabin's (1958) studies carried out in Cincinnati on summer diarrheal disease of infants clearly *established the role of the ECHO viruses in this disease.* They hasten to point out, however, that summer diarrheal disease may be a consequence of transitory infection *with a large variety of enteropathic bacteria, viruses, or both.*

The *enteroviruses* spread rapidly to other susceptible individuals, particularly within a family or a community. Illness is

rarely severe, and thus the hospitalized cases fail to reflect the size of the epidemic. In an epidemic in Milwaukee, only 149 cases were hospitalized in a city of 740,000 inhabitants, but a survey of the population indicated that 45,000 were ill with a similar illness which was determined to be ECHO virus, type 9, in the hospital cases. When normal children under five were surveyed enteric viruses were found three to six times more commonly in the children in the poorer districts of the city (Melnick, 1959).

The ECHO group of antigenically related [illegible] [illegible] in children and adults according to Sabin (1958). A respiratory enteric illness which was characterized by fever persisting for two days or less, rhinorrhea for six to nine days, serous discharge from the eyes, vomiting, and watery, malodorous stools has been observed during the winter months in infants under two years of age in association with ECHO virus, types 8 and 20 The latter was originally designated as JV-1, and discussed in more detail in the preceding paragraphs.

Although emphasis is being placed on the respiratory aspect of these viruses it is clear that there is a high incidence of aseptic meningitis caused by them with few or no paralytic manifestations Febrile illnesses occur with a high incidence of rash, especially in young infants, with or without a concomitant aseptic meningitis Diarrheal disease, too, in the very young infant is more than likely due to various strains of ECHO viruses and not associated with enteropathogenic bacteria

Diagnosis is accomplished readily by the isolation of the virus from stool or rectal swabs and cerebrospinal fluid. Several types, including 2, 4, 5, 6, 9, and 14, have been recovered from the spinal fluid of patients with aseptic meningi-

tis These isolations, as indicated previously, are most readily accomplished in kidney monolayer tissue culture from rhesus and cynomolgus monkeys. HeLa and other human cell culture lines have not been found suitable for primary isolations.

The *symptom picture of ECHO virus, type 16, disease (Boston exanthem)* has been summarized as follows: The age group includes children and adults, with an incubation period of four to five days; fevers range from 37.8° to 40° C, lasting only one to two days in patients without aseptic meningitis. *Mild sore throat, frequent abdominal pain, and rarely diarrhea* at the onset are the striking early symptoms, with vomiting occurring only in patients with aseptic meningitis. An exanthematous rash is common in children and less common in the adults, usually appearing after defervescence and disappearance of symptoms. *The rash is macular and maculopapular,* pink- or salmon-colored, discrete 1 mm to 1 cm macules most commonly appearing on the face, chest, and back and lasting two to four days. The enanthemata may be single or multiple, raised, red or yellowish-white lesions on the soft palate, tonsils, and uvula. This *symptom and sign* occurred in 50 per cent of the patients in the Pittsburgh epidemic. Aseptic meningitis is rarely due to ECHO virus, type 16, paralysis having occurred only in one sporadic case with no fatalities. *Spinal fluid findings* revealed that the leukocytes were usually less than 50 and not more than 100 with the white blood count in the peripheral blood being within normal limits. St. Geme and co-workers (1959) described 13 cases of rubelliform exanthem due to ECHO virus, type 9, *with fever, malaise, and gastrointestinal* symptoms. Pharyngitis, conjunctivitis, and cervical adenitis were recorded as occasional physical findings

SUMMARY

The ECHO viruses must now be considered as major etiologic agents in the production of diarrhea and various other human diseases These agents have now joined other infectious

agents as a cause of exanthemata and enanthemata. Certain of the ECHO viruses, types 8, 10, and 20, play a special role in respiratory illnesses prevalent during the colder months of the year. Many of the first 20 types of ECHO viruses have been known to invade the human nervous system and produce the syndrome of aseptic meningitis. According to Sabin (1958), to date the ECHO viruses cannot be accused of causing persistent paralysis or encephalitic sequelae.

No disease entity has been described for many of the *enteroviruses*, and many produce inapparent disease (Melnick, 1958). The disease entities caused by them are shown in the accompanying Table 4.

Table 4 *

DISEASES ASSOCIATED WITH ENTEROVIRUSES

Polioviruses	Paralysis (complete to slight muscle weakness) Aseptic meningitis Undifferentiated febrile illness, particularly during the summer
Coxsackie viruses, group A	Herpangina (types 2, 4, 5, 6, 8, 10) Undifferentiated febrile illness, particularly during the summer Aseptic meningitis (types A-7, A-9) Febrile illness with rash (type A-9)
Coxsackie viruses, group B	Aseptic meningitis Pleurodynia (Bornholm disease) [illegible] ... neo- [illegible]
ECHO viruses	[illegible] the summer Mild paralysis (?) (types 6 and 9) or encephalitis (type 9) Summer diarrhea of infants and children (type 18 and others)

* By permission of S Karger, Basel, 1958 (See reference under Berger, E, and Melnick, J L [1958])

REFERENCES

Beeman, E. A.; Huebner, R. J.; and Cole, R. M. (1952): Studies of Coxsackie viruses, *Am. J. Hyg.*, 55:83.

Beeman, E. A.; Parrott, R. H ; and Cole, R. M. (1951): Simultaneous occurrence of two immunological types of group A "Coxsackie" virus in a case of herpangina, *Proc. Soc. Exper. Biol. & Med.*, 78:295.

Berger, E., and Melnick, J. L. (1958): *Progress in Medical Virology*. Hafner Publishing Co , New York

Breese, B B. (1941): Aphthous pharyngitis, *Am. J. Dis. Child.*, 61.669.

Cardelle, G., Martin Jimenez, R.; Embil, J., Jr.; and Cao, F. (1954). Herpangina (reporte de 43 casos y aislamiento ded virus Coxsackie), *Rev. cubana pediat.*, 26:70.

Cole, R. M.; Bell, J. A ; Beeman, E. A ; and Huebner, R. J. (1951): Studies of Coxsackie viruses: Observations on epidemiological aspects of group A viruses, *Am J. Pub Health*, 41:1342.

Committee on the ECHO Viruses (1955): Enteric cytopathogenic human orphan (ECHO) viruses, *Science*, 122:1187.

Cramblett, H G , Rosen, L , Parrott, R. H.; Bell, J. A.; Huebner, R J ; and McCullough, N. B. (1958): Respiratory illness in six infants infected with a newly recognized ECHO virus, *Pediatrics*, 21 168.

Curnen, E. C., and Melnick, J L. (1951): Poliomyelitis and Coxsackie viruses in paralytic poliomyelitis, *Pediatrics*, 8 237

Dalldorf, G (1949). Coxsackie group of viruses (comment), *Science*, 110 594

Dalldorf, G (1951). Sparing effect of Coxsackie virus infection on experimental poliomyelitis, *J Exper Med*, 95 65

Dalldorf, G (1955) The Coxsackie viruses, *Ann. Rev. Microbiol.*, 9 277

Dalldorf, G (1957) Brief review of Coxsackie viruses in 1956, *Ann. New York Acad Sc*, 67 209

Dalldorf, G (1958). Coxsackie viruses, *Mod Med*, 26 83

Dalldorf, G.; Sickles, G. M; Plager, H.; and Gifford, R. (1949): Virus recovered from feces of "poliomyelitis" patients pathogenic for suckling mice, *J. Exper. Med*, **89**·567.

David, J. K., Jr; Leavitt, D; and Howitt, B F. (1951). Vesicular pharyngitis, its relationship to the Coxsackie group of viruses, *Pediatrics*, **8** 672.

Dodd, K, Johnson, L. M, and Buddingh, G J (1938). Herpetic stomatitis, *J. Pediat*, **12**·95

ECHO Viruses, National Foundation for Infantile Paralysis, Inc (1955): Enteric cytopathogenic human orphan (ECHO) viruses, *Science*, **122**.1187

Francis, T, Jr (1955) *Evaluation of 1954 Field Trial of Poliomyelitis Vaccine* (Summary Report). The National Foundation for Infantile Paralysis, New York

Fox, T G, and Murphy, A M. (1953). Herpangina with isolation of the virus, *New Zealand M. J*, **52** 257.

Fukumi, H, and Yokota, T (1953). Distribution of the Coxsackie group of viruses in Japan, *Jap J. M Sc & Biol*, **6** 201

Gard, S, and Johnsson, T (1952) Studies of Coxsackie viruses, *Acta path et microbiol. scandinav (suppl)*, **93** 332

Grulee, C G, and Panos, T C (1948) Epidemic poliomyelitis in children, *Am J Dis Child*, **75** 24

Huebner, R J, Armstrong, C, Beeman, E A, and Cole, R M (1950) Studies of Coxsackie viruses, preliminary report on occurrence of Coxsackie virus in a southern Maryland community, *J A M A*, **144** 609

Huebner, R J, Beeman, E A, Cole, R M, Biegelman, P M, and Bell, J A (1952) The importance of Coxsackie viruses in human disease, particularly herpangina and epidemic pleurodynia, *New England J Med*, **247** 249.

Huebner, R J, Cole, R M, Beeman, E A, Bell, J A, and Peers, J H (1951) Herpangina, etiological studies of a specific infectious disease, *J A M A*, **145** 628

Johnsson, T (1954) Family infections by Coxsackie viruses, *Arch ges Virusforsch*, **5** 384

Johnsson, T (1955) Occurrence of Coxsackie virus infections in an epidemic of poliomyelitis. *Arch. ges Virusforsch.*, **6**.216.

Johnsson, T. (1955): The occurrence of Coxsackie virus in a hospital material of paralytic poliomyelitis, aseptic meningitis and a miscellaneous group of diseases, *Arch. ges Virusforsch*, 6:250.

Johnsson, T., and Lindahl, J. (1953): Herpangina; a clinical and virological study, *Arch ges. Virusforsch.*, 5:96.

Jordan, W. S, Jr.; Stevens, D.; Katz, S.; and Dingle, J. H. (1956): A study of illness in a group of Cleveland families IX Recognition of family epidemics of poliomyelitis and pleurodynia during a search for respiratory-disease viruses, *New England J. Med.*, 258:687.

Karzon, D. T. (1957): Discussion: Part III. ECHO viruses, *Ann. New York Acad Sc*, 67.351.

Karzon, D. T; Barron, A. L; Winkelstein, W., Jr., and Cohen, S (1956): Isolation of agents other than poliovirus in seasonal aseptic meningitis. Read before the Society for Pediatric Research, Twenty-sixth Annual Meeting, Buck Hill Falls, Pa

Kasel, J. A; Cramblett, H. G, and Utz, J P (1958): Agents resembling enteroviruses isolated in HeLa cell cultures from fecal specimens, *Proc Soc Exper. Biol. & Med*, 99 703.

Kilbourne, E D (1952): Coxsackie viruses and human disease, *Am J M Sc*, 224:93

Kilbrick, S; Melendez, L; and Enders, J F (1957). Clinical associations of enteric viruses with particular reference to agents exhibiting properties of the ECHO group, *Ann New York Acad Sc*, 67.311

Kravis, L P; Hummeler, K, Sigel, M M, and Lecks, H I (1953) Herpangina: Clinical and laboratory aspects of an outbreak caused by group A Coxsackie viruses, *Pediatrics*, 11 113.

LeBouvier, G. L. (1954): Interference and cell protection by poliomyelitis virus in tissue culture, *Nature*, 174 649

Levine, H D; Hoer, S O, and Allanson, J C (1939) Vesicular pharyngitis and stomatitis, *J A M A*, 112 2020

Melnick, J. L (1953) The Coxsackie group of viruses, *Ann New York Acad Sc*, 56 587

Melnick, J L (1955) Tissue culture techniques and their appli-

cation to original isolation, growth, and assay of poliomyelitis and orphan viruses, *Ann New York Acad Sc*, 61:754.

Melnick, J. L. (1959): Enteroviruses, *Scient. American*, 200.89 (Feb).

Melnick, J. L, and Agren, K. (1952). Poliomyelitis and Coxsackie viruses isolated from normal infants in Egypt, *Proc Soc. Exper. Biol. & Med*, 81:621.

Melnick, J. L; Kaplan, A. S.; Zabin, E.; Contreres, G; and Larkum, N. W. (1951): An epidemic of paralytic poliomyelitis characterized by dual infections with poliomyelitis and Coxsackie viruses, *J. Exper. Med.*, 94·471

Melnick, J. L, Walton, M., and Myers, I. L. (1953): Isolation of a Coxsackie virus during a summer outbreak of acute minor illness, *Pub Health Rep*, 68 1178

Meyer, H, Jr; Roger, N.; Miesse, M; and Crawford, I (1957). Aseptic meningitis caused by orphan viruses and other agents, *Ann. New York Acad Sc.*, 67.332

Mitchell, S C., and Dempster, G. (1955) The finding of genital lesions in a case of Coxsackie virus infection, *Canad. M A. J*, 72·117.

Neva, F A (1956) A second outbreak of Boston exanthem disease in Pittsburgh during 1954, *New England J. Med*, 254 838

Neva, F A, and Enders, J F (1954) Cytopathogenic agents isolated from patients during an unusual epidemic exanthem, *J Immunol*, 72 307

Neva, F A, Feemster, R F, and Gorbach, I J. (1954). Clinical and epidemiological features of an unusual epidemic exanthem, *J A M A*, 155 544

Parrott, R H (1957) The clinical importance of group A Coxsackie viruses, *Ann New York Acad Sc*, 67 230

Parrott, R H (1957). Newly isolated viruses in respiratory disease, *Pediatrics*, 20 1066

Parrott, R H, *et al* (1954) Clinical and laboratory differentiation between herpangina and infectious (herpetic) gingivostomatitis, *Pediatrics*, 14:122

Parrott, R H, Huebner, R J, McCullough, N B, Wolf, S I;

and Naiden, E. (1955): The hospital as a factor in assessing the occurrence of Coxsackie viruses in various illness groups. I. Children from the outpatient department and various hospital wards, *Pediatrics*, 15:255.

Parrott, R. H.; Huebner, R. J.; and Rice, E. C (1953): The occurrence of Coxsackie viruses in hospitalized poliomyelitis patients, *Clin. Proc. Child. Hosp.*, 9:134.

Parrott, R. H.; Ross, S.; Burke, F. G ; and Rice, E. C. (1951): Herpangina; clinical studies of a specific infectious disease, *New England J. Med.*, 245:275.

Parrott, R. H ; Ross, S ; Burke, F. G.; and Rice, E. C. (1952): Further observations on herpangina and its relation to the Coxsackie group of viruses, *Clin. Proc. Child. Hosp*, 8:118.

Poliomyelitis Vaccine Evaluation Center (1955): Evaluation of 1954 field trials of poliomyelitis vaccine (summary report), *Am J. Pub. Health*, 45:1 (May 1955, Part 2).

Ramos-Alvarez, M , and Sabin, A. B. (1954): Characteristics of poliomyelitis and other enteric viruses recovered in tissue culture from healthy American children, *Proc. Soc. Exper. Biol & Med*, 87:655.

Ramos-Alvarez, M , and Sabin, A. B. (1958): Enteropathogenic viruses and bacteria, role in summer diarrheal diseases of infancy and early childhood, *J A M.A.*, 167:147.

Robbins, F C , Enders, J F , Weller, T H ; and Florentino, G L (1951): Studies on the cultivation of poliomyelitis viruses in tissue culture V The direct isolation and serological identification of virus strains in tissue culture from patients with non-paralytic and paralytic poliomyelitis, *Am J. Hyg.*, 54 286

Rasmussen, A. F ; Cline, F A ; and Borge, A F (1953): Coxsackie virus infections in northern Wisconsin, *Wisconsin M. J*, 52:129

Rhodes, A J , *et al* (1953) Studies on poliomyelitis in Ontario, *Canad. M.A J*, 68:438

Rhodes, A J , and Beale, A J (1957) Aseptic meningitis: Evidence for the etiologic role of Coxsackie B and "orphan" viruses, *Ann New York Acad. Sc.*, 67:212

Rhodes, A J.; Labzoffsky, N A.; Pantidou, M E., and Beale, A. J. (1956): The laboratory background of the Ontario Poliomyelitis Vaccination Study 1955, *Canad J Pub Health*, **47**·47.

Sabin, A B (1958): ECHO viruses, *Mod. Med.*, **26**·94.

St Geme, J W., Jr; Prince, J. T.; Scherer, W. F.; and Krivit, W. (1959): A clinical study of an exanthem due to ECHO virus type 9, *J. Pediat.*, **54**·459.

Salk, J. E (1958): Current trends in poliovirus activity, *Mod. Med.*, **26** 83

Salk, J. E.; Youngner, J S; and Ward, E N. (1954)· Use of color change of phenol red as the indicator in titrating poliomyelitis virus or its antibody in a tissue culture system, *Am. J Hyg.*, **60**.214.

Schall, L; Lennartz, H; and Hake, R (1956): Infektion mit Poliovirus Type II in einem Kinder- und Sauglingsheim, *Munchen. med. Wchnschr.*, **98** 1432

Scott, T F. McN, and Steigman, A J. (1941). Acute infectious gingivostomatitis, etiology, epidemiology and clinical picture of a common disorder caused by virus of herpes simplex, *J.A M A*, **117** 999

Shaw, E W, Melnick, J. L; and Curnen, E C (1950). Infection of laboratory workers with Coxsackie virus, *Ann Int Med*, **33** 32

Sobel, G, Aronson, B, Aronson, S, and Walker, D (1956) Pharyngoconjunctival fever report of epidemic outbreak, *Am J. Dis. Child.*, **92** 596

Stanley, N F; Dorman, D C; and Ponsford, J (1953) Studies on Australian strains of Coxsackie virus (groups A and B), *Australian J. Exper. Biol. & M Sc*, **31** 21.

Travassos, J (1953)· Occurrence of Coxsackie virus in Rio de Janeiro II Isolation of virus from infants with gastroenteric disturbances, *An Microbiol*, **2**.83

Travassos, J, *et al* (1953) Occurrence of Coxsackie virus in Rio de Janeiro I Preliminary studies on the isolation of the virus from feces and throat washings, *An. Microbiol*, **2**.71.

and Naiden, E. (1955): The hospital as a factor in assessing the occurrence of Coxsackie viruses in various illness groups. I. Children from the outpatient department and various hospital wards, *Pediatrics*, **15**:255.

Parrott, R. H.; Huebner, R. J.; and Rice, E. C. (1953): The occurrence of Coxsackie viruses in hospitalized poliomyelitis patients, *Clin. Proc. Child. Hosp.*, **9**:134.

Parrott, R. H.; Ross, S ; Burke, F. G.; and Rice, E. C. (1951): Herpangina; clinical studies of a specific infectious disease, *New England J. Med.*, **245**:275.

Parrott, R. H ; Ross, S.; Burke, F. G.; and Rice, E. C. (1952): Further observations on herpangina and its relation to the Coxsackie group of viruses, *Clin. Proc. Child Hosp.*, **8**:118.

Poliomyelitis Vaccine Evaluation Center (1955): Evaluation of 1954 field trials of poliomyelitis vaccine (summary report), *Am. J. Pub. Health*, **45**:1 (May 1955, Part 2).

Ramos-Alvarez, M , and Sabin, A. B (1954): Characteristics of poliomyelitis and other enteric viruses recovered in tissue culture from healthy American children, *Proc. Soc. Exper. Biol. & Med.*, **87**:655

Ramos-Alvarez, M , and Sabin, A. B (1958): Enteropathogenic viruses and bacteria, role in summer diarrheal diseases of infancy and early childhood, *J.A.M A* , **167**.147.

Robbins, F. C , Enders, J F , Weller, T. H , and Florentino, G. L. (1951) Studies on the cultivation of poliomyelitis viruses in tissue culture. V The direct isolation and serological identification of virus strains in tissue culture from patients with non-paralytic and paralytic poliomyelitis, *Am. J Hyg*, **54** 286

Rasmussen, A F , Cline, F A ; and Borge, A F (1953) Coxsackie virus infections in northern Wisconsin, *Wisconsin M J.*, **52**:129

Rhodes, A J , *et al* (1953). Studies on poliomyelitis in Ontario, *Canad M A J*, **68** 438

Rhodes, A J , and Beale, A J (1957): Aseptic meningitis Evidence for the etiologic role of Coxsackie B and "orphan" viruses, *Ann New York Acad Sc*, **67** 212

Rhodes, A J ; Labzoffsky, N. A ; Pantidou, M. E.; and Beale, A. J (1956): The laboratory background of the Ontario Poliomyelitis Vaccination Study 1955, *Canad. J Pub Health*, 47.47.

Sabin, A. B (1958): ECHO viruses, *Mod Med*, 26·94.

St. Geme, J W., Jr.; Prince, J T ; Scherer, W. F., and Krivit, W. (1959): A clinical study of an exanthem due to ECHO virus type 9, *J. Pediat.*, 54:459

Salk, J. E (1958)· Current trends in poliovirus activity, *Mod. Med*, 26 83.

Salk, J. E ; Youngner, J. S ; and Ward, E. N. (1954). Use of color change of phenol red as the indicator in titrating poliomyelitis virus or its antibody in a tissue culture system, *Am. J. Hyg.*, 60.214.

Schall, L ; Lennartz, H ; and Hake, R. (1956): Infektion mit Poliovirus Type II in einem Kinder- und Sauglingsheim, *Munchen med Wchnschr.*, 98 1432.

Scott, T. F McN., and Steigman, A J. (1941): Acute infectious gingivostomatitis, etiology, epidemiology and clinical picture of a common disorder caused by virus of herpes simplex, *J A M A*, 117 999.

Shaw, E W., Melnick, J L ; and Curnen, E C. (1950): Infection of laboratory workers with Coxsackie virus, *Ann. Int Med*, 33.32

Sobel, G , Aronson, B , Aronson, S ; and Walker, D (1956): Pharyngoconjunctival fever. report of epidemic outbreak, *Am J Dis Child*, 92 596

Stanley, N F ; Dorman, D. C.; and Ponsford, J. (1953): Studies on Australian strains of Coxsackie virus (groups A and B), *Australian J. Exper. Biol & M. Sc.*, 31:21

Travassos, J (1953). Occurrence of Coxsackie virus in Rio de Janeiro II Isolation of virus from infants with gastroenteric disturbances, *An. Microbiol*, 2 83.

Travassos, J , *et al* (1953). Occurrence of Coxsackie virus in Rio de Janeiro I. Preliminary studies on the isolation of the virus from feces and throat washings, *An Microbiol*, 2 71

and Naiden, E. (1955): The hospital as a factor in assessing the occurrence of Coxsackie viruses in various illness groups. I. Children from the outpatient department and various hospital wards, *Pediatrics*, **15**:255.

Parrott, R. H.; Huebner, R. J.; and Rice, E. C. (1953): The occurrence of Coxsackie viruses in hospitalized poliomyelitis patients, *Clin. Proc. Child. Hosp.*, **9**:134.

Parrott, R. H.; Ross, S.; Burke, F. G.; and Rice, E. C. (1951): Herpangina; clinical studies of a specific infectious disease, *New England J. Med.*, **245**:275.

Parrott, R. H.; Ross, S.; Burke, F. G.; and Rice, E. C. (1952): Further observations on herpangina and its relation to the Coxsackie group of viruses, *Clin. Proc. Child. Hosp.*, **8**:118.

Poliomyelitis Vaccine Evaluation Center (1955): Evaluation of 1954 field trials of poliomyelitis vaccine (summary report), *Am. J. Pub. Health*, **45**:1 (May 1955, Part 2).

Ramos-Alvarez, M., and Sabin, A. B. (1954): Characteristics of poliomyelitis and other enteric viruses recovered in tissue culture from healthy American children, *Proc. Soc. Exper. Biol. & Med.*, **87**:655.

Ramos-Alvarez, M., and Sabin, A. B. (1958): Enteropathogenic viruses and bacteria, role in summer diarrheal diseases of infancy and early childhood, *J.A.M.A.*, **167**:147.

Robbins, F. C.; Enders, J. F.; Weller, T. H.; and Florentino, G. L. (1951). Studies on the cultivation of poliomyelitis viruses in tissue culture. V. The direct isolation and serological identification of virus strains in tissue culture from patients with non-paralytic and paralytic poliomyelitis, *Am. J. Hyg.*, **54**:286.

Rasmussen, A. F.; Cline, F. A.; and Borge, A. F. (1953): Coxsackie virus infections in northern Wisconsin, *Wisconsin M. J.*, **52**:129.

Rhodes, A. J., *et al.* (1953). Studies on poliomyelitis in Ontario, *Canad. M. A. J.*, **68**:438.

Rhodes, A. J., and Beale, A. J. (1957). Aseptic meningitis. Evidence for the etiologic role of Coxsackie B and "orphan" viruses, *Ann. New York Acad. Sc.*, **67**:212.

Rhodes, A J.; Labzoffsky, N. A ; Pantidou, M E.; and Beale, A J. (1956): The laboratory background of the Ontario Poliomyelitis Vaccination Study 1955, *Canad. J. Pub. Health*, 47,47.

Sabin, A B. (1958): ECHO viruses, *Mod Med.*, 26:94

St. Geme, J W., Jr.; Prince, J. T.; Scherer, W. F ; and Krivit, W. (1959): A clinical study of an exanthem due to ECHO virus type 9, *J. Pediat.*, 54:459

Salk, J. E. (1958): Current trends in poliovirus activity, *Mod Med*, 26.83

Salk, J. E ; Youngner, J. S ; and Ward, E. N (1954): Use of color change of phenol red as the indicator in titrating poliomyelitis virus or its antibody in a tissue culture system, *Am J. Hyg.*, 60,214

Schall, L ; Lennartz, H ; and Hake, R. (1956): Infektion mit Poliovirus Type II in einem Kinder- und Sauglingsheim, *Munchen. med Wchnschr.*, 98 1432.

Scott, T. F. McN., and Steigman, A. J. (1941): Acute infectious gingivostomatitis; etiology, epidemiology and clinical picture of a common disorder caused by virus of herpes simplex, *J A M.A.*, 117:999.

Shaw, E W.; Melnick, J L ; and Curnen, E. C. (1950): Infection of laboratory workers with Coxsackie virus, *Ann. Int. Med.*, 33·32

Sobel, G.; Aronson, B , Aronson, S ; and Walker, D. (1956). Pharyngoconjunctival fever: report of epidemic outbreak, *Am J Dis. Child*, 92 596

Stanley, N F., Dorman, D. C ; and Ponsford, J (1953). Studies on Australian strains of Coxsackie virus (groups A and B), *Australian J. Exper. Biol. & M. Sc*, 31:21.

Travassos, J (1953): Occurrence of Coxsackie virus in Rio de Janeiro. II Isolation of virus from infants with gastroenteric disturbances, *An Microbiol.*, 2,83.

Travassos, J , *et al* (1953): Occurrence of Coxsackie virus in Rio de Janeiro I. Preliminary studies on the isolation of the virus from feces and throat washings, *An Microbiol.*, 2:71.

found in the acute serum specimen. This, however, may be obliterated by heating to 56° C for 30 minutes. Antibodies do not exist in individuals living in dengue-free areas; thus the finding of antibodies in such a patient recovering from an acute illness is presumptive evidence of infection.

Forty-seven distinct *arborviruses* have been classified into groups A, B, and C with many of the agents falling into the ungrouped classification. Group A includes the eastern, Venezuelan, and western equine encephalomyelitis, and group B includes dengue, types 1 and 2, Japanese B, Russian spring-summer, St. Louis, yellow fever and others. Colorado tick fever, Rift valley fever, and phlebotomus or sandfly fever still remain in the ungrouped classification. The hemagglutination-inhibition (HI) test has been found to be the most conclusive for the detection of serologic overlaps in the *arborviruses* The present grouping is based fundamentally on the behavior of these agents and their immune sera in the HI test Viruses which do not fall into any of the three groups (A, B, or C) will be classified by the name of the virus rather than adding further groups (Work, 1959)

PHLEBOTOMUS FEVER

This virus disease is characterized by fever and severe headache, with pain in the eyes, conjunctival injection, malaise, and leukopenia The illness has also been termed sandfly fever because biting insects belonging to the genus *Culicoides* have been called sandflies. In Italy, the ase is referred to as pappataci fever Th appea pecifically related to the insects *Phle* heref me seems appropriate at the presen

Geogra hic dist this egarded as im- ited areas *hle* *patasii* i an artic art , Afri Asi wee 4 Phlel

fever unlike dengue does not appear to invade new territories, but large outbreaks have occurred among troops or immigrants of countries free from the malady who have moved into infected areas. Hospital admissions among the U S. Army for phlebotomus fever number about 12,000, but many other fevers of unknown origin undoubtedly have been included. Control measures must be directed against the vector; DDT sprays are effective against *Phlebotomus papatasii.*

In man, the bite of the sandfly produces a small, itching papule which persists up to five days. The incubation period is approximately three to six days. Clinical manifestations consist of headache, malaise, nausea, fever, conjunctival injection, photophobia, stiffness of the neck and back, abdominal pain, and leukopenia. Sore throat, epistaxis, chills, and profuse sweating with weakness, especially during convalescence, also characterize the illness. The body temperature usually rises to a peak within 24 or 48 hours and then begins to fall The pulse rate is elevated in proportion to the fever, and bradycardia may be present at the end of the febrile period A rash such as that seen in dengue fever does not occur in phlebotomus fever Little is known regarding the basic pathologic picture as no fatalities among uncomplicated cases have been reported No specific treatment is available

COLORADO TICK FEVER

Colorado tick fever is a mild febrile disease without rash that is transmitted by a tick and caused by a virus of the arbor group as yet unclassified or ungrouped in either A, B, or C The virus is transmitted by the bite of the infected tick and is present in the blood during the acute stage of illness No pathology is known for this viral infection The incubation period is from four to six days, and the clinical features are characterized by a sudden onset with chills and aches, and include the influenza-like symptoms of headache, eye pain,

backache, nausea, and vomiting. The fever is usually diphasic. The white blood count may fall to leukopenic levels, but no complications have been recorded.

Specific complement-fixing antigens are available, and antibodies appear during the second week of the disease and persist for two or three years. The Weil-Felix reaction is negative. The disease is limited to the areas inhabited by the wood tick *Dermacentor andersoni*, they include Colorado, Oregon, Utah, Idaho, Montana, and Wyoming. The wood tick is the true reservoir of the virus, but it has also been isolated from dog ticks collected on Long Island even though human cases have not been known to occur in that area. Control measures include search for ticks and their prompt removal from the body.

Complement-fixing and hemagglutination-inhibition antibody tests are both methods which have been employed to confirm the diagnosis. Both types of antigens should be used to rule out or confirm infection. The hemagglutination-inhibition antibodies are the first to appear and may be present one week following the onset of illness. There is no specific treatment for Colorado tick fever.

REFERENCES

Bancroft, T L (1906) On the etiology of dengue fever, *Australasian M. Gaz*, 25:17.

Casals, J (1957). Viruses. The versatile parasites I The arthropod-borne group of animal viruses. *Tr New York Acad Sc.*, 19.219

Chandler, A. C., and Rice, L. (1923): Observations on the etiology of dengue fever, *Am. J Trop Med*, 3 233

Cleland, J. B ; Bradley, B ; and MacDonald, W (1919) Further experiments in the etiology of dengue fever, *J Hyg* 18 217

Fairley, N H. (1945)· Medicine in jungle warfare, *Proc Roy Soc. Med.*, 38:195.

Hanson, H (1936): Some observations on dengue, *Am J Trop Med.*, 16·371

Jawetz, E.; Melnick, J. L.; and Adelberg, E. H. (1958): *Review of Medical Microbiology*, 3rd ed. Lange Medical Publications, Los Altos, Calif.

Koizumi, T.; Yamaguchi, K.; and Tonomura, K. (1917): An epidemiological study of dengue fever, *J. M. A. Formosa* (nos. 176–177); abstract in *Trop. Dis. Bull.* (1918), 12:77.

MacCallum, F, and Dwyer, J. P. (1927): Dengue as a cause of death, *M. J. Australia*, 1:10

Sabin, A B (1944, 1945, 1946): Unpublished studies on dengue reported to Office of Surgeon General, U S. Army.

Sabin, A B (1948): Dengue: In Rivers, T. M, ed, *Viral and Rickettsial Infections of Man* J. P. Lippincott, Philadelphia, p 445.

Sabin, A B (1948): Phlebotomus fever: In Rivers, T. M, ed, *Viral and Rickettsial Infections of man*. J. P. Lippincott, Philadelphia, p 454

Sabin, A. B, and Schlesinger, R. W. (1945): Production of immunity to dengue with virus modified by propagation in mice, *Science*, 101 640

Sabin, A. B., and Schlesinger, R. W (1944, 1945, 1946): Unpublished studies on dengue reported to Office of Surgeon General, U S. Army.

Shortt, H. E ; Rao, R. S ; and Swaminath, C. S (1936) · Cultivation of the viruses of sandfly fever and dengue fever on the chorioallantoic membrane of the chick embryo, *Indian J. M. Res.*, 23 865

Siler, J G (1935). Dengue fever: In E B McKinley, *The Geography of Disease*. George Washington University Press, Washington, D C., pp. 402–8.

Stewart, F H (1944): Dengue: Analysis of the clinical syndrome at a South Pacific advance base, *U S. Naval M. Bull*, 42·1233.

Work, Telford (1959). Personal communication

Yaoi, H. (1958): A summary of our studies on dengue, *Yokohama M Bull.*, 9 1

Chapter Seven

MEASLES, DISTEMPER, AND PRIMARY PNEUMONITIS IN INFANTS

INTRODUCTION

The reason for including measles and distemper in the same chapter is that a parallelism appears to exist between these two virus diseases Although evidence for cross-infection taking place is still anecdotal, epidemiologic and clinical features of both diseases are quite similar, including almost identical incubation periods in their natural hosts, man and dog The pathologic picture, which has been studied in detail, is likewise almost identical, with the appearance of characteristic inclusion bodies in the cytoplasm as well as in the nucleus of infected cells in both of these diseases Experimentally some evidence of cross-neutralization has been demonstrated in low titer However, the natural viruses, as studied in the laboratory, have certain differences which as yet cannot be fully explained

MEASLES (RUBEOLA)

Measles undoubtedly holds the number one position as the first acute primary respiratory disease of man known to be

caused by a virus As early as 1759, Home transmitted the disease directly from man to man by means of bandages soaked in the blood of patients taken in the early stages of the disease. Hektoen, in 1905, successfully transmitted measles by subcutaneous inoculation of blood from patients, producing the typical disease with the correct incubation period Animal transmission experiments were successful in 1911, and Plotz cultivated the virus of measles in tissue culture in 1938. Further success was accomplished by Rake and Shaffer (1939), who cultivated the virus in embryonated chicken eggs. In 1954 Enders and Peebles propagated an agent from patients with measles which produced a characteristic pathologic change in various tissue cultures. This contribution has made it possible to study the virus from many points of view and will undoubtedly lead to the development of successful vaccines.

Epidemiology

A pattern of periodicity can be detected in the public health records of which there are now a great many, indicating a two- to three-year interval between epidemics of measles. Although the same interval is seen in the epidemic pattern of influenza, the pandemic nature of influenza is more evident than is the case in measles One community may have its measles epidemic one year and a nearby community the following year, sparing the previously involved community almost completely This is not the pattern of epidemic influenza

The cause of periodicity is not clearly established as yet, but most studies would favor the idea that epidemics are caused by the accumulation of large new groups of susceptible children A very high percentage of the population appears to exhibit frank measles, and second cases of measles are quite rare Authentic second attacks are recorded in the world literature, and a few individuals have been said to have regular measles

Chapter Seven

MEASLES, DISTEMPER, AND PRIMARY PNEUMONITIS IN INFANTS

INTRODUCTION

The reason for including measles and distemper in the same chapter is that a parallelism appears to exist between these two virus diseases. Although evidence for cross-infection taking place is still anecdotal, epidemiologic and clinical features of both diseases are quite similar, including almost identical incubation periods in their natural hosts, man and dog. The pathologic picture, which has been studied in detail, is likewise almost identical, with the appearance of characteristic inclusion bodies in the cytoplasm as well as in the nucleus of infected cells in both of these diseases. Experimentally, some evidence of cross-neutralization has been demonstrated in low titer. However, the natural viruses, as studied in the laboratory, have certain differences which as yet cannot be fully explained.

MEASLES (RUBEOLA)

Measles undoubtedly holds the number one position as the first acute primary respiratory disease of man known to be

caused by a virus As early as 1759, Home transmitted the disease directly from man to man by means of bandages soaked in the blood of patients taken in the early stages of the disease. Hektoen, in 1905, successfully transmitted measles by subcutaneous inoculation of blood from patients, producing the typical disease with the correct incubation period. Animal transmission experiments were successful in 1911, and Plotz cultivated the virus of measles in tissue culture in 1938. Further success was accomplished by Rake and Shaffer (1939), who cultivated the virus in embryonated chicken eggs In 1954 Enders and Peebles propagated an agent from patients with measles which produced a characteristic pathologic change in various tissue cultures This contribution has made it possible to study the virus from many points of view and will undoubtedly lead to the development of successful vaccines.

Epidemiology

A pattern of periodicity can be detected in the public health records of which there are now a great many, indicating a two- to three-year interval between epidemics of measles. Although the same interval is seen in the epidemic pattern of influenza, the pandemic nature of influenza is more evident than is the case in measles One community may have its measles epidemic one year and a nearby community the following year, sparing the previously involved community almost completely This is not the pattern of epidemic influenza.

The cause of periodicity is not clearly established as yet, but most studies would favor the idea that epidemics are caused by the accumulation of large new groups of susceptible children A very high percentage of the population appears to exhibit frank measles, and second cases of measles are quite rare. Authentic second attacks are recorded in the world literature, and a few individuals have been said to have regular measles

on many occasions Great interest is developing in the mechanism for prolonged or lifetime immunity which apparently exists in this disease.

Although the measurable titer of antibodies against measles is not of a high order and waning of the titer can be shown to occur in a few months to a year, immunity appears to be as solid as for any disease which we recognize. Sharp differences in clinical severity are probably associated with the presence of secondary complicating bacteria in the community. Serious complications are now well controlled by the availability of antibiotics, and the rare complication of measles encephalitis remains by far the most serious problem that exists with measles today.

Some variability in the age incidence is recognized, largely on the basis of the segregation of certain communities In the large urban centers the age incidence is lower and most children are involved with measles in the preschool years, whereas in the more rural communities children may escape an attack of this disease until young adulthood. In World War I, the bringing together of young men from rural communities resulted in several serious measles epidemics Second attacks of measles occur rarely, and many of these are probably related to other exanthematous diseases.

Weller (1958) points out that there has been a rapid development of our knowledge regarding the causes of many of the exanthemata in the last five years. These diseases are appearing along with the rapid-fire discovery of many new viral agents as a result of tissue culture methods Several of the newly discovered enteric viruses cause illnesses associated with a rash. One of the first of these to be described was Boston exanthem, which is now recognized as due to ECHO virus type 16. Another ECHO virus, type 9, produces a characteristic exanthem, particularly in children, whereas older individuals and adults have a rash much less frequently It is also

possible that certain of the Coxsackie agents rarely produce a rash. The German measles or rubella agent is not clearly defined, and infectious mononucleosis is another disease which occasionally may have an exanthem but etiologically remains in the realm of the unknown.

Clinical Features

The first symptoms of measles appear 10–12 days following exposure, with the rash appearing almost exactly on the fourteenth day when a clear-cut exposure is recognized. Measles is characterized by three stages: the first being the incubation period; the second, the prodromal period, at which time an enanthem known commonly as Koplik's spots occurs on the buccal mucosal membranes. Conjunctivitis and a rising temperature with running nose and cough make their appearance during this stage. At the height of the illness and fever (the final stage) a maculopapular rash erupts, appearing first on the face and body and subsequently spreading to the arms and hands with fading occurring in the areas where it first appeared There are many commonly recognized features of the measles rash which are almost pathognomonic. The blotchy nature of this rash, when associated with Koplik's spots and signs of conjunctivitis, coryza, and cough, leaves little doubt in the clinician's mind regarding the diagnosis. The centrifugal progression of the rash is extremely important as drug eruptions and other confusing eruptions fail to spread and fade in the same manner as measles, which leaves behind a pigmentation with a branny desquamation considered highly characteristic

Koplik's spots usually appear prior to the development of the eruption and may develop many days before the appearance of external rash. These spots are grayish-white with a slightly red areola, occasionally they may be hemorrhagic They appear first opposite the lower molars on the buccal

mucous membranes but then spread throughout the mouth. They may on occasion be confused with other enanthemata, including those seen in scarlet fever and rubella.

The clinical symptoms of coryza, cough, and conjunctivitis gradually increase in severity throughout the prodromal period and along with the fever reach a peak at the time when the body is nearly completely involved by the exanthemata. The fever frequently rises to 40°–40.6° C, and the blood picture may show a relative lymphocytosis with leukopenia. Recovery is often rapid and remarkable, and in a day or two a very sick patient may appear well on the road to recovery. Complications in the past have been common and should always be watched for closely. Convulsions may occur, ushering in the complication of encephalitis.

In the differential diagnosis rubella is frequently confusing but may be distinguished largely by the appearance of postcervical and postauricular lymph nodes. The nodes frequently appear in German measles prior to the onset of rash and may be the chief complaint of the patient. German measles or rubella is further distinguished from regular measles by the absence of striking respiratory symptoms, many patients exhibiting none of the rhinorrheal, conjunctival, or cough symptoms which are so classic in rubeola.

In the clinical spectrum of disease, we have come to recognize the presence of so-called atypical pneumonia in a small percentage of patients, and Dingle and associates on the Respiratory Commission (1944) showed a close parallelism between the incidence of acute respiratory disease (ARD) and atypical pneumonia. When an epidemic of rubella involved the camp, they could demonstrate no increase in the incidence of atypical pneumonia, strongly suggesting that this agent does not have a predilection for the respiratory passages. Because of the rash, however, rubella is extremely important in differential considerations. Scarlet fever frequently may be dif-

ferentiated on the basis of the character and location of the rash, which is increased in the bodily folds and is usually not on the face where it occurs so characteristically in patients with measles.

Exanthem subitum is characterized by a rash which appears along with the abrupt subsidence of fever, whereas in regular measles we recognize that the rash is maximum at the height of the fever. Drug rashes may at times be difficult to distinguish, but usually a history of intake is extremely helpful. A history of exposure to measles or some other illness should not be forgotten as an important aid to the clinician in making a differential diagnosis.

The chief complications of this disease as pointed out are encephalitis and the occurrence of otitis media and pneumonia; although the latter conditions are frequently related to secondary bacterial organisms they may also be a part of the disease itself and caused by the virus. The measles virus has been isolated from certain patients with giant cell pneumonia, with and without rash, and it is important to remember that in certain epidemics the incidence of pneumonia may be high indeed and related directly to the measles virus. The advent of antibiotics has served to clarify the role of the secondary bacterial invader, but unfortunately rare individuals may still die of an overwhelming pulmonary infection in spite of adequate antibiotic therapy. Many of these fatalities are undoubtedly related to the measles virus per se since a characteristic picture of giant cell pneumonia with inclusion bodies is almost pathognomonic of measles Giant cell pneumonia is discussed in Chapter Nine in greater detail

The cause of measles encephalitis is still unknown but is considered by many to be directly related to the measles virus. Although this virus has been difficult to obtain from patients with encephalitis, the methods of isolation and study in the past have not been as adequate as they are today It is possible,

without a rash. Many second cases of measles occurring years later have been mild and often associated with patients who have had previous inoculations with gamma globulin. Stokes (1959) suggests that 10 to 20 times the usual amounts of gamma globulin will modify the disease even when injected in the prodromal stage and suggests that at least the dangers of complications may be lessened. For the most part immunity acquired following gamma globulin seems to be of a rather permanent nature. Second cases of measles are extremely rare even following modification procedures.

Treatment

Treatment of uncomplicated measles is largely confined to the use of antipyretics and mild sedatives, which may include codeine mixtures for the relief of severe cough. Complete bed rest and adequate fluid intake are considered very helpful. Strong, bright light should be avoided, but otherwise no harm is done from ordinary light and a much cheerier environment may result. Complications should be watched for closely, and treatment with appropriate antibiotics administered when indicated. The routine use of antibiotics in the treatment of uncomplicated measles is not recommended even for prophylaxis of secondary complications. Weinstein (1955) was able to show that complications may not be prevented with any degree of assurance by penicillin but might even be increased when it is employed routinely for prevention. The emergence of organisms such as *Hemophilus influenzae* (bacillus) was the primary cause of bacterial complications in his reported series. Certainly the familiar incidence of streptococcal and pneumococcal complications is reduced, and this may be highly desirable in certain patients. However, as a rule such complications may be treated promptly and effectively when they arise

CANINE DISTEMPER

Jenner in 1809 was probably the first to compare distemper with the infectious fevers of man. Canine distemper has been recognized in most countries of the world as a common respiratory disease of dogs It was considered to be caused by certain bacteria and *Bacillus bronchisepticus* in particular for many years; but in 1905 Carré was able to transmit the disease by means of bacteria-free filtrates. The Field Distemper Council (Laidlaw and Dunkin) reported their studies on the cause of distemper in 1926 and clearly confirmed that distemper was caused by a specific virus. *Bacillus bronchisepticus* and other organisms were then recognized as secondary complicating agents.

Many different strains of distemper were isolated by Laidlaw and Dunkin (1926) but all were of a single type and cross-immunized against each other. They concluded that distemper was transmitted by filter-passing agents which produced no growth in ordinary culture media and "belonged to the class of filter-passing viruses" Evidence that the disease was first transmitted to man was contributed by Nicollé (1931), who reported that man might acquire the disease in inapparent forms In his experiments, man, monkeys, and dogs were inoculated at the same time with known strains of distemper virus As the disease manifested itself in experimental animals, material taken from human beings at the same time produced disease in normal puppies Nicollé interpreted his findings as evidence of an inapparent infection in man and concluded that man can serve as a reservoir of virus for animals, or vice versa

There are many other observations on the transmission of respiratory disease from man to dogs; one of the interesting reports is that of Bryan in 1928, who was able to transmit an infection from himself to puppies which within 7 to 10 days

"went down with the typical picture of canine distemper." He presented evidence of cross-infection between 11 children, all of whom presented signs of an acute respiratory disease following contact with acute distemper. "House dog disease" has been described by Whitney (1943) as a pharyngolaryngotracheitis which dogs contract from human beings.

Clinically, distemper is a highly contagious disease which primarily involves the respiratory passages. Puppies are highly susceptible, and during epidemics there may be a high fatality rate. Certain strains of virus appear to cause "hard pad disease," which is often associated with clinical forms of distemper. Infectious material from dogs with "hard pad disease" when transmitted to ferrets has produced a disease that clinically and pathologically appears identical with canine distemper. Montgomerie (1956) has indicated that there are definite strain differences between the "hard pad" agent and the virus that causes distemper.

The symptomatology of the puppy or ferret with respiratory distemper is similar in many ways to the classic symptoms recognized in measles, coughing and sneezing being striking symptoms with runny nose and signs of conjunctivitis. A rash is evident about the face and on the abdomen where it is most easily recognized. Encephalitis may be associated with the disease as a complication and would appear to be a common and serious form of the disease in puppies, particularly at times of epidemics. The exact incidence of encephalitis as a complication of canine distemper is difficult to determine but has been estimated as high as 5 per cent

Vuori (1946) reported a 21-year-old patient with transient paralysis of facial muscles, diplopia, and nystagmus, with stiff neck, hyperesthesia, and exaggerated reflexes, all of which developed following intimate contact with a dog suffering from the encephalitic form of distemper. The author states that he suspected that the illness may have been related in some way to canine distemper.

PRIMARY PNEUMONITIS IN INFANTS

Our interest in presenting distemper is aroused by the possibility that one of man's common respiratory diseases may be closely related to canine distemper. In 1950 it was demonstrated that serum from human beings was capable of neutralizing experimental distemper in animals and in the chick embryo. Prior to this discovery, however, a striking similarity between the pathologic picture presented by distemper in ferrets and a respiratory disease of human beings was known.

An epidemic disease was first recognized among newborn and prematurely born infants in January, 1937. The clinical features of cough and sneezing, which in many patients became severe, leading to dyspnea, cyanosis, and death, were uniformally observed in the original epidemic. Although the febrile responses were in general low grade, many of the patients had a high, spiking, biphasic type of fever curve. In one institution, extreme contagiousness was evident by the fact that every baby developed varying degrees of acute respiratory disease.

Attention was naturally directed to the severely ill babies with pneumonitis and bronchiolitis, but a review of the epidemic features soon indicated that all of the babies were suffering from acute respiratory disease which was mild in a few patients Thorough bacteriologic studies were performed, and no uniform organisms were found; although a few of the patients had some of the higher types of pneumococci, these were not associated with death At the time of the epidemic, a nonbacterial disease was suspected, and fresh frozen lung specimens were sent directly to Dr Thomas Francis, Jr, for influenza studies (1937). An influenza virus could not be identified as the cause of the epidemic.

In the most severely ill patients, fine rales were heard over the entire lung area but dullness was rarely elicited. Roentgenographic studies revealed evidence of overaeration with flat

diaphragms so characteristically seen in infants with bronchiolitis.

Unique and uniform pathologic findings were observed in the lungs of all of the babies who died. These consisted of destructive and proliferative changes in the bronchial epithelium with peribronchial infiltration of mononuclear cells. The epithelial cells lining the pulmonary tree contained characteristic cytoplasmic inclusion bodies which later were identified as being similar in all respects to those found in other viral diseases. Green and Evans (1939) described the inclusions as *"identical to those seen in distemper." They also pointed out* the significance of vacuolization within the inclusion bodies seen in the patients as well as those found in distemper. Giant cells were recorded, particularly in the finer bronchioles in many of the patients. These findings are discussed in greater detail in Chapter Nine under "Giant Cell Pneumonia," but the relationship of giant cells seen in distemper and human measles is indeed striking

The giant cells contain characteristic inclusion bodies which may involve the nucleus as well as the cytoplasm The classic description of distemper as recorded by several authors points out the interstitial pneumonia with peribronchial involvement and infiltration of mononuclear cells. De Monbreun (1937) describes inclusion bodies as seen in the lungs of dogs with distemper as follows.

> In all cases, cytoplasmic inclusion bodies were found *in both* bronchial and alveolar cells In some bronchi they are especially abundant They were situated in definite vacuoles and appeared well defined, usually round to oval, sometimes elongated Vacuolated acidophilic bodies *most often lie* between the nucleus and the outer margin of the cell, but sometimes at the opposite poles of the cell

In the photomicrographs, Figure 11, typical cytoplasmic inclusion bodies are illustrated from a baby under one year of

age with acute pneumonitis. The upper picture is made from a pharyngeal smear and shows the typical bipolar position of cytoplasmic bodies as well as several smaller inclusions. The lower picture is from a smear of sediment from the urine showing an epithelial cell with similar changes to those seen in the pharyngeal smear.

Recent experimental studies reveal that pathologic changes in animals and tissue cultures caused by distemper virus and measles virus have many similarities Giant cell formation with inclusion bodies is seen in the uncomplicated pathologic picture produced by these agents.

IMMUNOLOGIC STUDIES

Although the pathologic similarities between a human disease and distemper were striking, it was considered highly important to determine and compare the neutralizing properties of distemper antiserum with the serum from human subjects In the early studies, chicken embryos were used in which the successful cultivation of canine distemper virus was possible (Haig, 1948). An exudative lesion was produced by the distemper virus on the chorioallantoic membrane, and this lesion was in turn neutralized specifically by certain samples of human serum Several lots of human gamma globulin were shown to have a high titer against the distemper virus Normal ferrets were found to have no protective antibodies and died of distemper when challenged Immune ferrets, however, demonstrated antibody levels as high as 1:640 and successfully withstood a challenge of 100 minimum lethal doses (MLD) of distemper virus

Samples of serum from adult human beings have also shown protective titers as high as 1 640 (Imagawa *et al*, 1954) Data from 100 random samples from human sources showed that 44 per cent of sera had neutralizing substances at a titer of less than 1 20 Titers of 1 320 or greater were found in 20 per cent of the samples tested, and 9 per cent of sera showed

diaphragms so characteristically seen in infants with bronchiolitis.

Unique and uniform pathologic findings were observed in the lungs of all of the babies who died. These consisted of destructive and proliferative changes in the bronchial epithelium with peribronchial infiltration of mononuclear cells. The epithelial cells lining the pulmonary tree contained characteristic cytoplasmic inclusion bodies which later were identified as being similar in all respects to those found in other viral diseases. Green and Evans (1939) described the inclusions as "identical to those seen in distemper." They also pointed out the significance of vacuolization within the inclusion bodies seen in the patients as well as those found in distemper. Giant cells were recorded, particularly in the finer bronchioles in many of the patients. These findings are discussed in greater detail in Chapter Nine under "Giant Cell Pneumonia," but the relationship of giant cells seen in distemper and human measles is indeed striking

The giant cells contain characteristic inclusion bodies which may involve the nucleus as well as the cytoplasm The classic description of distemper as recorded by several authors points out the interstitial pneumonia with peribronchial involvement and infiltration of mononuclear cells De Monbreun (1937) describes inclusion bodies as seen in the lungs of dogs with distemper as follows

> In all cases, cytoplasmic inclusion bodies were found in both bronchial and alveolar cells In some bronchi they are especially abundant They were situated in definite vacuoles and appeared well defined, usually round to oval, sometimes elongated Vacuolated acidophilic bodies most often lie between the nucleus and the outer margin of the cell, but sometimes at the opposite poles of the cell

In the photomicrographs, Figure 11, typical cytoplasmic inclusion bodies are illustrated from a baby under one year of

age with acute pneumonitis. The upper picture is made from a pharyngeal smear and shows the typical bipolar position of cytoplasmic bodies as well as several smaller inclusions. The lower picture is from a smear of sediment from the urine showing an epithelial cell with similar changes to those seen in the pharyngeal smear.

Recent experimental studies reveal that pathologic changes in animals and tissue cultures caused by distemper virus and measles virus have many similarities Giant cell formation with inclusion bodies is seen in the uncomplicated pathologic picture produced by these agents.

IMMUNOLOGIC STUDIES

Although the pathologic similarities between a human disease and distemper were striking, it was considered highly important to determine and compare the neutralizing properties of distemper antiserum with the serum from human subjects In the early studies, chicken embryos were used in which the successful cultivation of canine distemper virus was possible (Haig, 1948) An exudative lesion was produced by the distemper virus on the chorioallantoic membrane, and this lesion was in turn neutralized specifically by certain samples of human serum Several lots of human gamma globulin were shown to have a high titer against the distemper virus. Normal ferrets were found to have no protective antibodies and died of distemper when challenged. Immune ferrets, however, demonstrated antibody levels as high as 1:640 and successfully withstood a challenge of 100 minimum lethal doses (MLD) of distemper virus

Samples of serum from adult human beings have also shown protective titers as high as 1.640 (Imagawa *et al.*, 1954) Data from 100 random samples from human sources showed that 44 per cent of sera had neutralizing substances at a titer of less than 1 20 Titers of 1.320 or greater were found in 20 per cent of the samples tested, and 9 per cent of sera showed

titers of 1:640. Serum samples from 12 normal premature infants showed protective substances at 1:20 dilution but not at 1:40. Karzon's studies (1955) on neutralizing antibodies against distemper revealed that normal newborns have a positive titer which disappears between 6 and 12 months of age and is again acquired by children in the preschool and school years, during which time the titers rise to levels comparable to those found in adults and in the newborn.

Further reports by Carlstrom (1956 and 1957) clearly demonstrate that children's sera are capable of neutralizing canine distemper virus Carlström employed mice in her neutralization tests, and clear protection was evident from the sera of older children and adults, but infants under four years of age rarely showed antibodies with the exception of the newly born. Prier, Wright, and Kalter (1956) demonstrated distemper complement-fixing antibodies in human as well as animal sera.

Measles (rubeola) and canine distemper must still be considered as distinct clinical entities, but certain relationships exist between them As pointed out earlier in this chapter, the incubation periods, which are well known in both diseases, appear to be similar Both diseases are considered highly contagious and primarily affect the respiratory passages. The outstanding symptoms and signs are those of fever, cough, coryza, and conjunctivitis Although it is difficult to compare the rash in human beings with that in animals, there is no doubt that a

---

Figure 11. These two photomicrographs are of epithelial cells The upper cell (1) was taken from the pharyngeal area of a baby acutely ill with pneumonitis the lower cell (2) is from the urinary tract of the same baby, obtained from fresh urinary sediment They both illustrate typical cytoplasmic inclusion bodies with two bodies seen in the bipolar positions with several other smaller bodies in each cell The stain is hematoxylin and eosin No virus was isolated from this patient who recovered without complications (From Adams, J M, and Imagawa, D T [1955] Studies on the etiology of a human respiratory disease In Good, R A., and Platou, E S [eds] *Essays on Pediatrics in Honor of Dr Irvine McQuarrie*, Lancet Publications, Inc, Minneapolis)

Viremia was found in 100 per cent of the puppies between the second and eighth days following inoculation and passage. Experiments likewise showed viremia in 100 per cent of the animals, fever occurring in 65 per cent and rash in 40 per cent following passage from the initial experiment Antibodies capable of neutralizing the measles virus were demonstrated.

The details of the pathologic comparison between distemper and measles have been presented in the literature and will not be further elaborated here. However, the clinical finding of Warthin-Finkeldey cells in the early stages of measles is comparable to giant cell formation caused by distemper infection in ferrets Two such cells are shown in Figure 12 for comparison. A characteristic clumping together of cells with spider-like filaments extending between cells and the formation of giant cells is considered highly characteristic of the pathologic changes in tissue culture produced by the measles virus Giant cells in particular but also other cells contain characteristic intranuclear as well as cytoplasmic inclusion bodies Figure 13 illustrates these changes in the lung of a child who died of measles pneumonia

A study of the preimmunization serum in ferrets failed to show any inhibition of the measles virus in tissue culture, whereas serum from ferrets immunized with distemper virus showed a protection in tissue culture in low titers ranging from 1·2 to 1.8 Attempts to protect ferrets immunized with pure strains of measles virus from challenge by distemper were considered only partially successful Among the 20 experimental animals there were 8 survivors and 12 deaths, only 1 animal survived among 18 control ferrets The serum from the one surviving control ferret which received only distemper virus showed a rise in measles antibody from zero to 1:8. Experiments with the mouse-adapted distemper virus mixed with specific measles antiserum showed a sound protection but in low titer Three hundred minimum lethal doses (MLD) of



①



②

mouse-adapted distemper virus and undiluted measles antiserum mixtures were inoculated intracerebrally into one- to two-day-old mice. The experimental animals were completely protected from the lethal effects of the virus demonstrated in the control animals. Dilution studies at 1:4 reveal some protection as well (Adams and Imagawa, 1957).

Measles Immunization

In November, 1952, prior to the recognition of a relationship between distemper and measles, a pilot vaccination study was carried out with live distemper virus. This study was initiated because of a possible relationship between acute respiratory disease in humans and canine distemper. The finding of specific antibodies in human beings against distemper indicated a possible relationship to one of man's respiratory illnesses With these thoughts in mind 200 individuals were given a specially prepared live distemper vaccine grown in chick embryos. Two hundred additional subjects were given an influenza polyvalent vaccine prepared in eggs, and an avianized strain of mumps vaccine was given to 200 further subjects

The epidemiology of measles was well recorded in the institution, and an epidemic occurred in March, April, and May of 1952, six months prior to the administration of the vaccine Although an epidemic of rubella occurred in 1953, no cases of measles of any kind were reported during the year 1954, The next epidemic of regular measles (rubeola) occurred in

---

Figure 12. These two photomicrographs illustrate giant cells The upper cell (1) was seen in the pharyngeal smear of a child with regular measles (rubeola) and shows typical cytoplasmic inclusion bodies with striking pleomorphism and the typical clear zone about each body This is a classic Warthin-Finkeldey cell In the lower picture (2) the giant cell was seen in the pharyngeal smear from a ferret which was acutely ill with distemper. Inclusion bodies contain small dark granules occasionally seen in inclusion bodies of this type Arrows point to inclusion bodies (Adams J M, Imagawa, D T, Chadwick, D L, Gates, E H, and Siem, R A [1958] Relationship of measles and distemper, *A M A J Dis. Child*, 95 604)


1
2

the latter half of 1955, almost three years following the giving of the vaccine

In the course of this epidemic approximately 11 per cent of the patients in the institution were involved The patients remaining in the institution who had previously been inoculated in the late 1952 were studied for the incidence of measles Data were available on approximately 165 individuals in each of these three groups; the results showed that the distemper-inoculated subjects had more than a threefold reduction in the incidence of measles when compared to the two other control groups, in whom the incidence was similar to that recorded in the institution Although the significance of this degree of reduction is not apparent at the present time, the fact that the challenge experience occurred almost three years following but a single inoculation may indicate some degree of protection. In order to follow up this possible means of vaccination against measles, a program of immunization of half of the new patients being admitted to another hospital has been inaugurated. It may be possible following the next epidemic of measles to determine the protective effect of a live distemper vaccine prepared in eggs and inoculated subcutaneously. No untoward effects were observed from the use of this vaccine in the 200 subjects previously inoculated in 1952. Some mild local reactions were recorded which may well have

---

Figure 13. These two photomicrographs were made from lung sections of a baby who died of measles (rubeola) The upper picture (1) reveals a large giant cell with about 15 to 20 nuclei, most of which show heavy margination and typical intranuclear inclusion bodies The other pleomorphic bodies in the cytoplasm are typical cytoplasmic inclusion bodies (From Adams, J M, and Imagawa, D T [1956] Giant cell pneumonia, clinicopathologic and experimental studies, *Pediatrics*, 18 893)

The lower picture (2) is from the same baby's lung and shows epithelial cells with single inclusion bodies in them, seen in the cytoplasm at one end of the nucleus Arrows point to the inclusions Close inspection will reveal vacuoles, granules, and a slight halo about each body (From Adams, J M, and Imagawa, D T [1957] The relationship of canine distemper to human respiratory disease, *Pediat Clin North America*, 3 197)

been related to varying degrees of egg sensitivity, but no severe systemic reactions occurred.

SUMMARY

The clinical similarities between measles and distemper have been compared as well as the epidemiologic features of these two diseases. The incubation periods appear to be almost identical, and the pathologic findings have many features in common, including the occurrence of intranuclear as well as cytoplasmic inclusion bodies in epithelial lining cells of the lung Giant cell formation occurs in both diseases.

The measles virus has been readily adapted to various tissue culture preparations whereas great difficulty has been encountered in attempts to adapt the distemper virus to these same tissues. Laboratory animals, however, may now be infected by these viruses, and the intracerebral inoculation of mice has provided a common host in which to continue further studies of the relationship Recently, distemper virus has been grown in dog kidney tissue culture where it produces giant cells similar to those seen in tissue cultures infected with measles virus.

Common antigenic components are apparently shared by the viruses of measles and distemper. The final relationship between canine distemper and human respiratory disease will have to await further studies in the laboratory

A preliminary immunization study with a single inoculation of live avianized distemper virus has shown a threefold reduction in the incidence of measles The significance of this finding can only be determined by further field studies which are now in progress

REFERENCES

Adams, J M (1941) Primary virus pneumonitis with cytoplasmic inclusion bodies: Study of epidemic involving thirty-two infants with nine deaths, *J.A M A* , 116 925

Adams, J. M. (1953): Comparative study of canine distemper and a respiratory disease of man, *Pediatrics*, **11**:15.

Adams, J M ; Green, R. G ; Evans, C A ; and Beach, N (1942): Primary virus pneumonitis: Comparative study of two epidemics, *J. Pediat*, **20**·405.

Adams, J M., and Imagawa, D. T. (1955): Studies on the etiology of a human respiratory disease: In *Essays on Pediatrics*. Lancet Publications, Minneapolis.

Adams, J. M , and Imagawa, D T. (1957). Immunological relationship between measles and distemper viruses, *Proc. Soc. Exper Biol & Med*, **96**.240.

Adams, J. M , and Imagawa, D T. (1957): The relationship of canine distemper to human respiratory disease, *Pediat. Clin. North America*, **3**.193

Adams, J. M., Imagawa, D T ; Wright, S W., and Tarjan, G (1959) Measles immunization with live avian distemper virus, *Virology*, **7** 351

Adams, J M , Imagawa, D. T.; Yoshimori, M , and Huntington, R W (1956) Giant cell pneumonia; clinical and experimental studies, *Pediatrics*, **18** 888

Black, F L , Reissing, M , and Melnick, J L (1956) Propagation of measles virus in a strain of human epidermoid cancer cells (Hep-2), *Proc Soc. Exper Biol. & Med*, **93** 107

Bryan, A H (1928). Canine distemper, danger to children, *Vet Med*, **23** 396

Cabasso, V P , and Cox, H R (1949) Propagation of canine distemper virus in the chorioallantoic membrane of embryonated hen eggs, *Proc. Soc. Exper Biol & Med.*, **71** 246

Carlstrom, G (1956) Appearance in children's sera of substances capable of neutralizing canine distemper virus, *Acta paediat*, **45** 180

Carlstrom, G (1957). Neutralization of canine distemper virus by serum of patients convalescent from measles (letter to the editor), *Lancet*, **2**·344.

Carre H (1905) Sur la maladie des jeunes chiens, *Acad Sc*, **140** 689

Coffin, D L , and Liu, C (1957) Studies on canine distemper infection by means of fluorescein-labeled antibody II The

pathology and diagnosis of the naturally occurring disease in dogs and the antigenic nature of the inclusion body, *Virology*, 3:132.

Corbett, E. U. (1945): The visceral lesions in measles, with a report of Koplik spots in the colon, *Am. J. Path.*, 21:905

Dekking, F., and McCarthy, K. (1956): Propagation of measles virus in human carcinoma cells, *Proc. Soc. Exper. Biol. & Med.*, 93.107.

De Monbreun, W. A. (1937). Histopathology of natural and experimental canine distemper, *Am. J. Path.*, 13:187.

Denton, J. (1925): Pathology of fatal measles, *Am. J. M. Sc.*, 169.531.

Enders, J F., and Peebles, T. C. (1954): Propagation in tissue cultures of cytopathogenic agents from patients with measles, *Proc. Soc Exper. Biol. & Med.*, 86:277.

Finkeldey, W (1931): Uber Riesenzellbefunde in den Gaumenmandeln, zugleich ein Beitrag zur Histopathologie der Mandelveranderungen in Maserninkubationstadium, *Arch. path Anat.*, 281 323

Gordon, H, and Knighton, H T (1941). Experimental measles. Lymphoid tissues of animals inoculated with the virus of human measles, *Am. J. Path*, 17 165

Green, R G, and Evans, C A (1939) Rapid diagnosis of canine distemper, *Cornell Vet*, 29:35

Haig, D A (1948) Preliminary note on the cultivation of Green's distemperoid virus in fertile hen eggs, *Onderstepoort J Vet. Sci & Animal Industry*, 23 149

Hecht, V. (1910) Die Riesenzellanpneumonie in Kindersalter, *Beitr path Anat*, 48 263

Imagawa, D T, Yoshimori, M, Wright, S W, and Adams, J M (1954) Serum neutralization of distemper virus in chick embryo, *Proc Soc Exper Biol & Med* 87 2

Imagawa, D T, and Adams, J M (1958) Propagation of measles virus in suckling mice, *Proc Soc Exper Biol & Med*, 98 567

Jenner, E (1809-11) Observations on the distemper in dogs. *Med-Chir Tr*, 1-2 263

Karelitz, S., and Isenberg, H. D. (1959): The antibiotic prophylaxis of bacterial complications of measles, *J. Pediat.*, **54**:1

Karzon, D. T. (1955). Studies on a neutralizing antibody against canine distemper virus, *Pediatrics*, **16**:809

Kromayer, E. (1889): Uber die sogenannte Katarrhalpneumonie nach Massern und Keuchhusten, *Arch. path. Anat.*, **117**:452

Laidlaw, P. P., and Dunkin, G. W. (1926): Studies in dog distemper, nature of virus, *J. Comp. Path. & Therap.*, **39**:220

Larin, N. M. (1955). Canine distemper virus in the ferret, *J. Comp. Path. & Therap.*, **65**:325

Liu, C., and Coffin, D. L. (1956). A study of canine distemper in ferrets and dogs by means of fluorescent antibody, *Fed. Proc.*, **15**:600

Liu, C., and Coffin, D. L. (1957). Studies on canine distemper infection by means of fluorescein-labeled antibody. I. The pathogenesis, pathology, and diagnosis of the disease in experimentally infected ferrets, *Virology*, **3**:115

Montgomerie, R. F. (1956). Personal communication

Morse, H. G., Chow, T. L., and Brandly, C. A. (1953). Propagation of a strain of egg-adapted distemper virus in suckling mice, *Proc. Soc. Exper. Biol. & Med.*, **84**:10

Moulton, J. E. (1956). Fluorescent antibody studies of demyelination in canine distemper, *Proc. Soc. Exper. Biol. & Med.*, **91**:460

Moulton, J. E., and Brown, C. H. (1954). Antigenicity of canine distemper inclusion bodies as demonstrated by fluorescent antibody technic, *Proc. Soc. Exper. Biol. & Med.*, **86**:99

Nicolle, C. (1931). La maladie du jeune age des chiens est transmissible expérimentalement à l'homme sous forme inapparente, *Arch. Inst. Pasteur Tunis*, **20**:321

Panum, P. L. (1940). *Observations Made during the Epidemic of Measles on the Faroe Islands in the Year 1846*. Delta Omega Society, New York

Pinkerton, H., Smiley, N. L., and Anderson, W. A. D. (1945). Giant cell pneumonia with inclusions. A lesion common to Hecht's disease, distemper and measles, *Am. J. Path.*, **21**:1

Prier, J. E., Wright, B. S., and Kalter, S. S. (1956). Detection of

complement-fixing antibodies for Carré's virus, *Science*, 123. 586.

Rake, G., and Shaffer, M. F. (1939): Propagation of the agent of measles in the fertile hen's egg. *Nature*, 144.672.

Riazantzeva, N. E. (1956): Experimental measles in puppies, *Zhur. Mikrobiol., Epidemiol., Immunobiol.*, 27:5.

Robertson, H E.; Brunner, K. T.; and Syverton, J. T. (1955). Propagation in vitro of poliomyelitis viruses VII pH change of HeLa cell cultures for assay, *Proc. Soc. Exper. Biol. & Med.*, 88.119.

Rockborn, G. (1958): Canine distemper virus in tissue culture, *Arch Virusforsch*, 8·485.

Ruckle, G. (1957): Studies with measles virus. I. Propagation in different tissue culture systems, *J Immunol.*, 78:330

Ruckle, G., and Rogers, K. D (1957). Studies with measles virus. II Isolation of virus and immunologic studies in persons who have had the natural disease, *J Immunol.*, 78 341.

Scherer, W F (1953. The utilization of a pure strain of mammalian cells (EARLE) for the cultivation of viruses in vitro I Multiplication of pseudorabies and herpes simplex viruses, *Am. J Path.*, 29 113.

Semsroth, K. H (1939). Multinucleate epithelial giant cells with inclusion bodies in prodromal measles Report of an autopsy, *Arch Path*, 28 386

Shaffer, M F, Rake, G, and Hodes, H L (1942) Isolation of virus *from a patient with fatal encephalitis complicating* measles, *Am. J Dis Child*, 64.815

Stokes, J (1959). *Measles, Textbook of Pediatrics*, 7th ed W B Saunders Co., Philadelphia, p 486

Taniguchi, T, Kamahora, J, Kato, S, and Higiwara, K (1954) Pathology in monkeys experimentally infected with measles virus, *M J Osaka University*, 5 367

Tompkins, V, and Macaulay, J C (1955) A characteristic cell *in nasal secretions during prodromal measles*, *J A M A*, 157 711

Vuori, E E (1946) Can distemper be transmitted to man? *Duodecim*, 52 23

Warthin, A. S (1931): Occurrence of numerous large giant cells in the tonsils and pharyngeal mucosa in the prodromal stage of measles: Report of 4 cases, *Arch Path*, **11**·864
Weinstein, L. (1955). Failure of chemotherapy to prevent the bacterial complications of measles, *New England J. Med.*, **253** 679.
Weller, T. H. (1958): Developments in our knowledge of the acute viral exanthemas, *Mod. Med.*, **26** 109.
Whitney, L. F. (1943)· House-dog disease, *Vet Med.*, **38** 419.

Chapter Eight

INFECTIOUS MONONUCLEOSIS, ACUTE INFECTIOUS LYMPHOCYTOSIS, AND LYMPHOCYTIC CHORIOMENINGITIS

INFECTIOUS MONONUCLEOSIS

Because of its name, attention has been directed to the mononuclear elements of the blood as the essential pathologic alteration of this disease; however, the primary disturbance appears to be in the lymphocytic cells. The importance of infectious mononucleosis as a respiratory disease will be emphasized as nearly all of the recent reports refer to the frequency of acute pharyngitis with or without membrane in this disease The cervical lymph nodes are almost uniformly involved, and it is evident that the differential diagnosis of acute tonsillitis and cervical adenitis would be incomplete without due consideration for infectious mononucleosis

The history of infectious mononucleosis has been divided into four periods by Houck (1949) These are characterized by the clinical description from 1885 to 1920, the period of description of the blood changes from 1920 to 1932, the in-

troduction of the Paul and Bunnell heterophil antibody test, 1932 to 1944; and the final period, pathologic description which dates from 1944 to the present time. Unfortunately, we do not as yet know the exact cause of infectious mononucleosis, but it is categorically regarded to be a virus disease, period five yet to be discovered

Clinical and Epidemiologic Features

The communicability of this disease is considered to be low, although epidemics occur, particularly in schools with a dormitory type of housing The age group characteristically seems to be the young adult, but older children may be involved and no age group is exempt The incubation period is approximately 11 days, although there is some variability. Fever, sore throat, and general malaise are the outstanding symptoms with enlargement of lymph nodes, particularly in the cervical chain, dominating the physical findings Not infrequently there may be a generalized lymphadenopathy, but little pain is complained of and the nodes rarely suppurate Lymph node enlargement may persist throughout the duration of the illness; the spleen is palpable in about 50 per cent of the patients, but this may not be evident during the first week of illness

A typical skin rash has been reported in as many as one-fifth of the patients and appears usually from the fourth to the tenth day of the disease The rash is described as a macular type of eruption which is most prominent over the trunk and may rarely assume a petechial or a vesicular appearance Jaundice is occasionally associated with this disease and indicates hepatic involvement Certainly in many patients with jaundice, infectious mononucleosis should be seriously considered Differentiating infectious mononucleosis from infectious hepatitis may be difficult, inasmuch as in the latter disease atypical lymphocytes have been described Liver in-

volvement also occurs in infectious mononucleosis as indicated by marked disturbances in the liver function tests with or without the appearance of jaundice. A recent study revealed 84 per cent of children with infectious mononucleosis to have disturbed liver function tests.

The central nervous system is infrequently involved, and the common symptomatology is related to headache, stiffness of the neck, some blurring of vision, mental confusion, and, rarely, convulsions. Spinal fluid changes are minimal with increase in mononuclear cells (probably lymphocytes) and protein. In addition to central nervous system and hepatic involvement, the heart has also been described as being involved in infectious mononucleosis. The relationship to rheumatic fever is referred to, and definite electrocardiographic changes are recorded. These largely consist of abnormal T waves with inversion, first pointed out by Longcope in 1922. The symptoms of cardiac involvement include fever, malaise, and pain across the chest and shoulders. Electrocardiographic changes may indicate the presence of acute pericarditis Collections of mononuclear cells and lymphocytes have been reported by Allen and Kellner (1947) in heart muscle These findings were subsequently confirmed by Brien (1947) and also by Custer and Smith (1948), who observed myocardial infiltrations in six of eight autopsied patients. A 19-year-old girl who died following rupture of the spleen from infectious mononucleosis showed focal collections of lymphoid cells in the heart, described in 1950 by Kass and Robbins.

Splenic pathology reveals the sinuses and pulp packed with large, abnormal lymphocytes described as having a neoplastic appearance. Smith and Custer (1946) reported seven cases of rupture of the spleen with four deaths The spleens appeared grossly enlarged and were soft and friable. The capsule showed infiltration with mononuclear cells. The authors caution the

clinician against the too frequent and vigorous palpation of the spleen in suspected cases of infectious mononucleosis. Splenic rupture would appear to be one of the common causes of death in an otherwise relatively benign disease.

Diagnosis

The disease has been associated with a disturbance in mononuclear cells which, according to Downey and McKinlay (1923), belong in the category of lymphocytes. They have divided these abnormal cells into three types. In type 1, the nucleus is oval or lobulated in shape and is usually eccentrically placed. The cytoplasm is deep blue and irregular with a mottled appearance. These represent the commonest type of abnormal lymphocytes. The type 2 cells are somewhat larger, and their nuclei have more regular shapes and certain coarse, distinct chromatin strands. The cytoplasm is lighter staining and less mottled, with irregular strands of deep blue staining material extending out from the nucleus to the periphery of the cell. The type 3 cells are said to resemble the lymphoblast of lymphocytic leukemia, but their nuclei tend to be regular in shape although disproportionately large. The small amounts of cytoplasm are quite basophilic. The total white blood count is often elevated, and predominance of lymphocytes is characteristic. Although the polymorphonuclear cells may make their appearance early, in a few days the lymphocytes dominate the picture and may constitute 60 to 90 per cent of the total leukocytes.

The heterophil antibody test will become positive, as a rule, during the first week of illness. Frequent tests should be made as rapidly changing titers may lead to confusion and the possibility of missing a positive agglutination. False positive tests have been said to occur in association with serum sickness, but rarely in acute infections. Modifications of the

volvement also occurs in infectious mononucleosis as indicated by marked disturbances in the liver function tests with or without the appearance of jaundice. A recent study revealed 84 per cent of children with infectious mononucleosis to have disturbed liver function tests.

The central nervous system is infrequently involved, and the common symptomatology is related to headache, stiffness of the neck, some blurring of vision, mental confusion, and, rarely, convulsions. Spinal fluid changes are minimal with increase in mononuclear cells (probably lymphocytes) and protein. In addition to central nervous system and hepatic involvement, the heart has also been described as being involved in infectious mononucleosis. The relationship to rheumatic fever is referred to, and definite electrocardiographic changes are recorded. These largely consist of abnormal T waves with inversion, first pointed out by Longcope in 1922. The symptoms of cardiac involvement include fever, malaise, and pain across the chest and shoulders. Electrocardiographic changes may indicate the presence of acute pericarditis. Collections of mononuclear cells and lymphocytes have been reported by Allen and Kellner (1947) in heart muscle. These findings were subsequently confirmed by Brien (1947) and also by Custer and Smith (1948), who observed myocardial infiltrations in six of eight autopsied patients. A 19-year-old girl who died following rupture of the spleen from infectious mononucleosis showed focal collections of lymphoid cells in the heart, described in 1950 by Kass and Robbins.

Splenic pathology reveals the sinuses and pulp packed with large, abnormal lymphocytes described as having a neoplastic appearance. Smith and Custer (1946) reported seven cases of rupture of the spleen with four deaths. The spleens appeared grossly enlarged and were soft and friable. The capsule showed infiltration with mononuclear cells. The authors caution the

clinician against the too frequent and vigorous palpation of the spleen in suspected cases of infectious mononucleosis. Splenic rupture would appear to be one of the common causes of death in an otherwise relatively benign disease.

Diagnosis

The disease has been associated with a disturbance in mononuclear cells which, according to Downey and McKinlay (1923), belong in the category of lymphocytes. They have divided these abnormal cells into three types. In type 1, the nucleus is oval or lobulated in shape and is usually eccentrically placed The cytoplasm is deep blue and irregular with a mottled appearance. These represent the commonest type of abnormal lymphocytes The type 2 cells are somewhat larger, and their nuclei have more regular shapes and certain coarse, distinct chromatin strands The cytoplasm is lighter staining and less mottled, with irregular strands of deep blue staining material extending out from the nucleus to the periphery of the cell. The type 3 cells are said to resemble the lymphoblast of lymphocytic leukemia, but their nuclei tend to be regular in shape although disproportionately large. The small amounts of cytoplasm are quite basophilic. The total white blood count is often elevated, and predominance of lymphocytes is characteristic. Although the polymorphonuclear cells may make their appearance early, in a few days the lymphocytes dominate the picture and may constitute 60 to 90 per cent of the total leukocytes

The heterophil antibody test will become positive, as a rule, during the first week of illness Frequent tests should be made as rapidly changing titers may lead to confusion and the possibility of missing a positive agglutination False positive tests have been said to occur in association with serum sickness, but rarely in acute infections Modifications of the

Paul and Bunnell (1932) test introduced by Barrett add appreciably to the accuracy of this diagnostic procedure. The differential absorption tests using guinea pig kidney and beef red cells greatly enhance the specificity. A titer of at least 1 to 30 following absorption is considered necessary for a diagnosis of infectious mononucleosis. Abnormal lymphocytes similar to those seen in infectious mononucleosis have been found in infectious hepatitis, primary atypical pneumonia, German measles (rubella), brucellosis, and certain allergic conditions. Sadusk (1941) reports that 15 per cent of patients with infectious mononucleosis may have a false positive complement-fixation test for syphilis. This appears during the second week in the majority of cases and may become negative within two weeks. It is reported to be higher in individuals who develop a rash than in those who do not have an eruption

Hoagland (1952), in reporting a series of young adults from West Point, emphasizes that 70 per cent of his patients complained of a sore throat. This was by far the commonest complaint, with malaise and headache occurring in 35 to 45 per cent of the patients. Lymph node tenderness was recorded in approximately 11 per cent. The finding of lymph node enlargement in 100 per cent of his patients is of particular significance in this present discussion, and he makes a strong point of the fact that 82 per cent of his patients exhibited pharyngeal and tonsillar inflammation This was described as severe in 40 per cent, moderate in 40 per cent, and mild in the remainder of the individuals Edema of the eyelids was a characteristic finding in the West Point series, occurring in 34 per cent of the subjects An enanthem was described in three subjects, jaundice in two, and relative bradycardia in two additional individuals In the series reported by Hoagland (1952) there were no patients with a rash

The prognosis of infectious mononucleosis is considered

good, even in patients with serious organ involvement such as liver and central nervous system. Weakness and fatigability, however, may persist for many weeks, and occasionally for many months. Although the liver function tests may remain abnormal for extended periods of time, there are as a rule no sequelae of significance except for very rare cases of chronic hepatitis. Fatalities have occurred in association with rupture of the spleen in the course of the acute illness. There is no specific treatment other than to watch for secondary complications. Bed rest in the acute febrile stages of the disease is considered important, and this, as a rule, is a matter of two or three weeks. Activity may then be started on a gradual basis and governed largely by the patient's fatigability. Persistently abnormal liver function tests do not indicate that the patient should be bedridden, provided he is free of other symptoms.

ACUTE INFECTIOUS LYMPHOCYTOSIS

Originally this condition was considered to be closely related to infectious mononucleosis but in 1941 it was described as a separate clinical entity by C. H. Smith. The clinical disease is characterized by marked increase in the total number of lymphocytes in the peripheral blood, and in some patients this may be the only clinical or laboratory manifestation. However, fever and signs of acute respiratory disease, including abdominal complaints, skin rashes, and meningoencephalitis have been closely associated. An entire family of six children presumably with this disease was suffering from an illness which the family described as "colds." The epidemic nature of the illness in this particular family appeared to be definite. Other epidemics have been described in institutions as well as families with a predilection for children. The disease has been observed in the Western Hemisphere as well as in Europe.

Clinical Features

The symptomatology of this disease has been characteristically mild, and in epidemics individuals have been found with high lymphocytic blood counts but with no signs of illness. Sore throat, vomiting, irritability, abdominal pain, and diarrhea have been the commonest symptoms Meningoencephalytic signs have also been rarely recorded in association with this ill-defined syndrome. Rashes of a morbilliform nature similar to those seen in infectious mononucleosis have been observed. The commonest manifestations appear to be those associated with mild respiratory disease. This is the main reason for including a brief discussion of this condition here. The only characteristic clinical pathologic finding is that of a high leukocytosis which may average 40,000 to 50,000 white blood cells per cubic milliliter and may reach as high as 100,000 cells. Lymphocytic cellular elements account for the increases with percentages running as high as 97 per cent. No abnormality is recognized in these elements, and the heterophil agglutination test is negative. The diagnosis is based on clinical manifestations and must be differentiated from infectious mononucleosis, leukemia, pertussis, and rarely other conditions in which the lymphocytes are sharply increased. Infectious mononucleosis may be differentiated by the serious nature of the infection as compared to acute infectious lymphocytosis and by the positive heterophil and abnormal lymphocytes which are so characteristic.

In pertussis, the severity of the illness as a rule correlates directly with the level of the lymphocytic cell counts, those with the highest counts representing the most severe cases Abnormally high counts may persist for several weeks and rarely may last for months The clinical picture of acute infectious lymphocytosis is very benign, and no mortality has been reported No specific treatment is indicated, and the prognosis is uniformly good

LYMPHOCYTIC CHORIOMENINGITIS

Discussion of lymphocytic choriomeningitis is included because of the evidence that this virus may produce an illness in man similar in many respects to undifferentiated respiratory disease. Our knowledge of the natural history of lymphocytic choriomeningitis is extremely limited, however, it was recognized early that the virus caused a grippe-like illness in laboratory workers The virus received its name originally because in experimental animals it produced inflammatory lesions of the choroid plexus. In random blood samples complement-fixing antibodies against lymphocytic choriomeningitis virus occurred in approximately 11 per cent of those tested, when analyzed for a history of recent respiratory disease, antibodies were found in 28 per cent of the subjects. Very few proved cases of lymphocytic choriomeningitis have been studied, and there is a surprising lack of pathologic information.

Smadel and co-workers (1942) reported a worker who, following exposure to the virus in the laboratory, became ill with ever, malaise, general aches, sore throat, vomiting, cough, nd leukopenia The illness persisted unabated until the paent died, at which time there were no signs of meningitis or icephalitis at autopsy. The lungs revealed patches of pneuonia which were characterized by mononuclear cell inflamtion The lymphocytic choriomeningitis virus was isolated m the blood and the brain tissues The second patient reted had assisted at the autopsy of the first patient, and eight ays later developed fever, leukopenia, and sore throat Acute respiratory signs developed which progressed to his death 17 days later with findings of acute necrotizing pharyngitis and pneumonia. Neither of the patients had lumbar punctures during life as clinically there appeared to be no indication. The lymphocytic choriomeningitis virus was isolated from the pulmonary tissues of the second patient.

The virus is known to occur naturally in several species including the common house mouse, guinea pigs, monkeys, and dogs and has been isolated from nasal secretions, and excretory and other material such as semen, urine, and feces of animals. A great deal needs to be learned regarding the respiratory manifestations of this disease, but preliminary evidence would indicate that it may have a place in the broad spectrum of the common respiratory diseases.

REFERENCES

Allen, F. H., Jr., and Kellner, A. (1947): Infectious mononucleosis, *Am. J. Path.*, **23**:463.

Bender, C. E. (1952): Diagnosis of infectious mononucleosis, *J.A.M.A.*, **149**:7.

Bernstein, A. (1940): Infectious mononucleosis, *Medicine*, **19**:85.

Bernstein, T. C., and Wolfe, H. G. (1950). Involvement of the nervous system in infectious mononucleosis, *Ann. Int. Med.*, **33**:1120.

Brien, F. S. (1947) Infectious mononucleosis—complications, *Canad. M. A. J.*, **56**:499.

Cohn, C., and Lidman, B. E. (1946) Hepatitis without jaundice in infectious mononucleosis, *J. Clin. Invest.*, **25**:145.

Custer, R. P., and Smith, E. B. (1948). The pathology of infectious mononucleosis in blood, *Blood*, **3**:830.

Darley, W., Black, W. C., Smith, C., and Good, F. A. (1944) Spontaneous splenic rupture in infectious mononucleosis. A case and pathologic report, *Am. J. M. Sc.*, **208**:381.

Downey, H., and McKinlay, C. A. (1923) Acute lymphadenosis compared with acute lymphatic leukemia, *Arch. Int. Med.*, **32**:82.

Hoagland, R. J. (1952) Infectious mononucleosis, *Am. J. Med.*, **13**:158.

Houck, G. H. (1949) Infectious mononucleosis, *Am. J. Med.*, **7**:699.

Houck, G. H. (1953) Involvement of the heart in infectious mononucleosis, *Am. J. Med.*, **14**:261.

Jordan, W. S, and Albright, R. W. (1950): Liver function tests in infectious mononucleosis, *J. Lab. & Clin Med.*, **35**:688.
Karpinski, F. E, Jr (1952). Neurologic manifestations of infectious mononucleosis in childhood, *Pediatrics*, **10**:265
Kass, E. H, and Robbins, S. L (1950). Severe hepatitis in infectious mononucleosis Report of a case with minimal clinical manifestations, and death due to rupture of the spleen, *Arch. Path*, **50**.644.
Kilham, L., and Steigman, A J. (1942)· Infectious mononucleosis, *Lancet*, **243**.452
King, R. B (1941). Spontaneous rupture of the spleen in infectious mononucleosis, *New England J. Med.*, **224**·1058
Leibowitz, S. (1952). Infectious mononucleosis. The value of differential absorption tests in its serologic diagnosis, *Am J. Med.*, **13**:172
Longcope, W. T (1922) Infectious mononucleosis (glandular fever), with a report of ten cases, *Am J M Sc*, **164** 781.
Mathisen, A K. (1952)· Hepatitis in infectious mononucleosis, *Canad M A J.*, **66**·426
Paul, J R, and Bunnell, W W (1932). The presence of heterophile antibodies in infectious mononucleosis, *Am J M Sc*, **183** 90
Sadusk, J F, Jr (1941) The skin eruption and false positive Wassermann in infectious mononucleosis, *Internat Clin*, **1** 239
Smadel, J E, Green, R. H, Paltauf, R. M, and Gonzales, T. A (1942) Lymphocytic choriomeningitis Two human fatalities following an unusual febrile illness, *Proc Soc Exp Biol & Med*, **49** 683
Smith, C H (1941). Infectious lymphocytosis, *Am J Dis Child*, **62** 231
Smith, C H (1944). Acute infectious lymphocytosis, *J A M A*, **125** 342
Smith, E B, and Custer, R P (1946) Rupture of the spleen in infectious mononucleosis A clinicopathologic report of seven cases, *Blood*, **1** 317
Soloff, L A, and Zatuchni, J (1953) Infectious mononucleosis

glutination have been of value in helping to confirm the diagnosis of primary atypical pneumonia.

With the advent of specific *antipneumococcus serum*, followed quickly by the sulfonamides and antibiotics, it became clear to many investigators that most of the bacterial pneumonias responded favorably to specific therapy. However, a large number of patients with pneumonia failed to respond; these were soon tabbed atypical pneumonia postulated to be due to, or presumably due to, viruses. A long list of agents, however, can be made and categorized as true virus pneumonia. When seen as individual cases differential diagnosis is most difficult unless associated with some specific epidemic or isolation of the causal agent is accomplished. Keefer and Hewitt (1955) have recorded a list of pneumonias which they consider to be due to viral agents. The list is as follows: influenza, smallpox, measles, chickenpox, lymphocytic choriomeningitis, the psittacosis-lymphogranuloma venereum group, ornithosis, SF virus disease, Kolmer's disease, Louisiana pneumonitis, Illinois virus, and meningopneumonitis. To this list we might add the *adenoviruses*, other new *myxoviruses*, and perhaps some of the *enteroviruses*. It is obvious from this long list that these viral agents do not always produce pneumonia but may be responsible for mild respiratory disease, and there is good evidence as well to substantiate inapparent infection by many of these viruses

PRIMARY ATYPICAL PNEUMONIA

Specific features of pneumonia have been discussed previously in chapters dealing with the various entities. This discussion will be focused on the pneumonias designated as primary atypical pneumonia still of unknown etiology. Although there is evidence that viruses are the major causal factors in this syndrome, success in growing a definite agent

from these patients has not been accomplished with regularity. Primary atypical pneumonia occurs sporadically and in epidemics, and most frequently during the winter months at a time when other respiratory diseases are also common. During World War II 10 to 20 per cent of the patients with acute respiratory disease in military camps were found to have this syndrome. Epidemics in colleges and other institutions were also recognized In 1937 we observed an epidemic of primary pneumonitis in infants which was highly contagious, involving every baby in the institution, but many of the patients were only mildly ill with coughing and sneezing. It is referred to here only to emphasize the clinical spectrum which was recognized at that time. In Chapter Seven, which is concerned with measles and distemper, this disease has been discussed in some detail.

In the case of measles and many other known agents it is clear that the same etiologic agent is involved in the patients with mild illnesses as in those who are severely ill and occasionally die The Respiratory Commission during World War II carried out extensive epidemiologic studies and very early emphasized the relationship of mild respiratory disease to the severe and widespread atypical pneumonias. In their volunteer studies a group of 13 of 48 inoculated subjects developed pneumonia, and 50 per cent of the remaining subjects developed acute illnesses of the respiratory system but without evidence of pneumonia. Further epidemiologic studies indicated that person-to-person transmission occurs commonly, and in family epidemics all degrees of involvement may be seen

Incubation periods have been variable, from 7 to 14 days Hilleman and associates (1955) have studied large epidemics of *adenovirus* infections, their studies have clearly demonstrated the wide clinical spectrum with 80 per cent of the

military population being involved, approximately one-half of these having inapparent or mild illnesses, another 20 per cent with severe illness, and approximately 20 per cent requiring hospitalization. In the latter group 15 per cent were diagnosed as having *adenovirus* pneumonitis. Undoubtedly many of these were included in the earlier epidemics during World War II and were diagnosed primary atypical pneumonia

Etiology

No single clear-cut virus has been found to be responsible for primary atypical pneumonia, and much of the confusion lies in the fact that there are probably many agents that produce this syndrome. As early as 1939, Stokes, Kenny, and Shaw reported the isolation of a filterable agent from two patients with pulmonary disease, but the agent was lost in subsequent passage experiments Horsfall and associates (1943) isolated an agent from four patients which was passed to the mongoose and chick embryo This agent was neutralized by convalescent serum from recovered patients Eaton, Meiklejohn, and van Herick (1944) likewise isolated an agent from the lung and sputum of patients which caused an infection in cotton rats and hamsters as well as chick embryos. They also demonstrated antibodies in the serum of convalescent patients and the presence of positive cold agglutinins and streptococcus MG agglutinins

In 1946 the Commission on Acute Respiratory Diseases of the Army Epidemiological Board carried out human volunteer studies with washings from patients with primary atypical pneumonia Seventy-five per cent of the inoculated subjects developed acute respiratory disease. About 25 per cent of these had signs of pneumonia, whereas the remaining subjects had varying forms of acute respiratory disease. They demonstrated a rise in cold agglutinins in 17 of 21 volunteers, in individuals with mild respiratory disease as well as pneumonia

Pathology

Studies of the pathology of primary atypical pneumonia are scanty because of the relatively low mortality, but the histopathologic picture of virus pneumonia is well recognized and varies to some degree with the offending agent. However, the primary infiltrative cell is usually mononuclear; the extent of the infiltration varies from minimal peribronchial involvement in some patients to extensive, almost consolidated lesions. Ulceration and necrosis of bronchial and bronchiolar epithelium may be associated with purulent and tenacious exudate. Hyperemia and edema of the bronchi and bronchioles constitute a prominent feature in association with the interstitial pneumonitis. Edema often extends into the alveolar areas which may be filled with fluid, mononuclear cells, and small amounts of fibrin.

Inclusion and elementary bodies are found in certain types of pneumonitis caused by known as well as unknown agents. In Figure 14, photomicrographs are shown from an infant who died from adenovirus, type 1, pneumonia. Proliferative changes are shown in a small bronchiole with a peribronchial mononuclear reaction. A typical cytoplasmic inclusion body was found in a lining epithelial cell in a bronchiole, shown in higher power in the lower picture and indicated by the arrow.

The formation of giant cells has occurred in various viral infections in the lung and other areas of the respiratory passages. These are found characteristically in measles pneumonia and in patients without obvious measles; there are now definite isolations of measles virus from patients without rash or other characteristic signs of measles (MacCarthy et al., 1958). A section of this chapter has been devoted to giant cell pneumonia, and the pathology of pneumonitis as seen in crib deaths is also reviewed later in this chapter.

1

2

Clinical Features

As a rule, the onset of primary atypical pneumonia is characterized by mild respiratory symptoms which are not as abrupt as may occur in typical lobar pneumonia or influenza. Signs of general malaise, fatigue, and weakness usually dominate the onset, and cough is nearly always present. In infants cough may be mild or absent; some babies will go for hours without demonstrating a cough. Sore throat, chest pain, and abdominal discomfort are associated with primary atypical pneumonia. Cough is seldom productive, but sputum may be streaked with bright red blood A certain proportion of patients complain of sore throat with sneezing and running nose. General malaise and muscle aching may be prominent symptoms, but as a rule these symptoms are milder than those commonly seen in influenza. Fever is usually present although in infants afebrile courses have been prominent. Wide swings in temperature are characteristic of this entity, and biphasic curves are recognized Duration of fever is variable but ranges from a few days to several weeks.

Red and dry throats are typical of these patients, who may have few other findings to account for their disability, fever, and general malaise. It is estimated that fewer than one-half of the patients demonstrate abnormal physical findings in the lungs on the initial examination However, thorough repeated examinations frequently will reveal fine crepitant rales which may change from time to time rather than remaining localized.

Figure 14. These two photomicrographs illustrate the histopathology of type 1 *adenovirus* pneumonia. The upper picture (1) shows a small bronchiole with hyperplasia, and a mononuclear cellular exudate The lower picture (2) illustrates a high-power view of bronchiolar lining cells with evidence of destruction and a typical cytoplasmic inclusion body at one end of the nucleus, indicated by the arrow. The latter finding is not typical as the inclusion bodies are usually intranuclear. (Courtesy of Dr Werner Henle, University of Pennsylvania)

Fine crackling rales associated with bronchiolitis are often characteristic. Chest x-ray shadows are usually mottled or ground glass in appearance but may actually involve only one lobe in association with atelectasis which may appear like consolidation. A picture of the x-ray of the lung from a child with a diagnosis of atypical pneumonia is shown (Fig. 15), with increased shadows of a ground-glass appearance on the left side. This four-year-old child's illness was diagnosed as

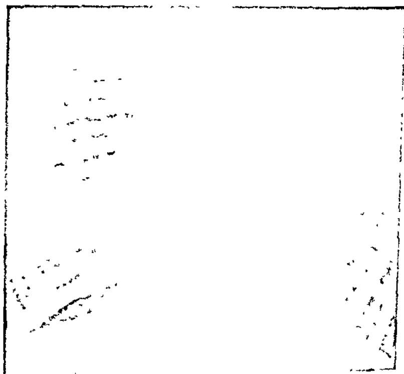


Figure 15. A roentgenogram of the chest of a four-year-old child with pneumonia, showing a soft shadow on the left side with increased bronchovascular shadows, most marked on the left. This child was exposed to a puppy with distemper. Paired serum samples revealed a negative titer in the early serum sample, and a titer of 1:160 against distemper in the convalescent serum sample. Influenza titers and cold agglutinins were negative.

pneumonitis and persisted with fever for five days Influenza antibody tests were negative as were the cold agglutinins. However, neutralization tests in chick embryos revealed no neutralization in the acute specimen and complete neutralization at 1·160 in the convalescent serum against canine distemper virus

In infancy, the diaphragm tends to be low in association with the viral types of bronchiolitis and pneumonitis, often with diminished infiltrative shadows. Other laboratory tests are of little value from the point of view of diagnosis. Serologic studies, however, have been very helpful in differentiating primary atypical pneumonia from other forms of pneumonitis. Agglutinins in the patient's serum occur in over half of the cases, but there is a direct correlation with severity of disease so that nearly all of the severe illnesses have positive cold hemagglutination reactions, falling to as low as 20 per cent in the milder illnesses This reaction varies from epidemic to epidemic. It is usually positive in the second week, and titers may vary from 1 40 to 1:640. Titers rarely persist longer than two months but may continue at high levels, particularly when convalescence is prolonged. Further serum antibody studies with streptococcus MG agglutinins may also be demonstrated in a high percentage of severely ill patients This antibody correlates well with the patients who have cold hemagglutination reactions. In the case of streptococcus MG, agglutinin titers of 1 4 or higher are considered of diagnostic significance.

These two antibody reactions have been demonstrated to be separate and distinct and therefore unrelated Serologic evidence would tend to incriminate the streptococcus MG which is one of the nonhemolytic strains as a possible etiologic factor in primary atypical pneumonia. However, frequent failures to isolate the organism from living patients as well as fatal cases, volunteer studies in which disease has been produced with

bacteria-free filtrates, and failure of patients to respond to specific treatment such as penicillin have all argued strongly against this organism as the etiologic agent.

Complications are not uncommon and are associated with secondary bacterial infections including all of the complications known to exist with bacterial diseases of the lung, such as emphysema and lung abscess. Fractured ribs have been reported due to violent coughing. Rarely, signs of central nervous system disease have been associated with meningoencephalitis or polyneuritis.

Diagnosis

Diagnosis is based primarily on the clinical course, with history and physical examination being the outstanding factors supported by roentgenologic and serologic evidence just referred to in the preceding paragraphs. Bacterial pneumonias are probably the most frequent diseases to be considered in the differential diagnosis. Certainly tuberculosis and fungal infections as well as Q fever must be considered in all patients with sporadic atypical pneumonia. The psittacosis-ornithosis group of viruses produce a similar picture These are discussed in Chapter Ten

Treatment

The management of primary atypical pneumonia has been almost entirely symptomatic and supportive with good nursing care Keefer and Hewitt (1955) state that "the prompt response within 24–48 hours of symptoms and fever to Aureomycin has provided very convincing, if not conclusive, evidence of the effectiveness of this agent in this disease" Similarly, chloramphenicol and oxytetracycline (Terramycin) have been found effective in many patients. Doses of 50 mg kilogram day given orally on a four to six hour schedule

are recommended until signs of improvement appear, at which time the dosage is decreased for three to five days.

Although the direct effect of antibiotics on atypical pneumonia, etiology undetermined, is difficult to be certain of, it remains a practical fact that in the presence of pneumonia they are usually given. The problem of mixed infection is a difficult one to solve, and a program of adequate antibiotic therapy therefore is almost without exception recommended in the presence of pneumonia.

BACTERIAL PNEUMONIAS

There is no limit to the problems of bacterial pneumonias which might be discussed if only by way of differential diagnosis. However, emphasis is being placed on the primary viral infections and related entities, and therefore the bacterial pneumonias will be mentioned only briefly. The list is a long one, but for the most part these pneumonias are considered secondary to primary infections with aspiration of infected material being the principal route of infection. This mechanism is discussed in Chapter One under the pathogenesis of respiratory tract infections.

The pneumococci head the list with types 1, 2, 3, 5, 7, and 8 being the commonest seen in adult life, types 19 and 14 are the common organisms found in infancy and early childhood. Streptococci, staphylococci, *Klebsiella pneumoniae*, and *Hemophilus influenzae* make up the common list with the following organisms accounting for uncommon bacterial pneumonias. *Bordetella pertussis*, *Bacillus anthracis*, *Pasteurella tularensis*, *Salmonella typhosa*, meningococcus, *Pseudomonas aeruginosa*, *Pasteurella pestis*, *Escherichia coli*, *Malleomyces mallei*, *Brucella melitensis*, and *Micrococcus catarrhalis*.

Acute inflammations of the lungs and pleura may occur in association with rheumatic fever. The pneumonitis is acute

with a patchy distribution throughout both lungs, associated frequently with pleurisy, with or without effusion. Signs of pericarditis may also be associated with the pleurisy of rheumatic pneumonia. Dyspnea and orthopnea are conspicuous symptoms and signs, and high irregular fevers which persist for weeks are the usual pattern. The diagnosis is relatively easy when associated with arthritis and other manifestations of acute rheumatic fever.

Erythema multiforme exudativum is frequently associated with pneumonitis and may actually lead to the patient's demise. The bullous lesions of the conjunctiva, mouth, and genitals usually facilitate making the diagnosis, and signs of primary atypical pneumonia should be looked for in these patients. The etiology of the pneumonia in association with erythema multiforme exudativum is unknown. Cold hemagglutinins, complement-fixation antibodies for psittacosis, and search for herpes virus should be made. Drug sensitivity appears to play a role in many patients, particularly to barbiturates and sulfonamides. Antibiotic therapy is usually recommended, primarily for control of any possible secondary infection

Loeffler's syndrome is unknown etiologically and pathogenically. However, it is generally considered to be due to an allergic condition with pulmonary infiltrations associated with eosinophilia, and many different infestations of a parasitic nature have been incriminated. Von Meyenburg (1942) studied three cases of accidental death and found foci of pneumonitis with eosinophils predominating as the infiltrative cell Symptomatology is not characteristic and may simulate many forms of atypical pneumonitis The diagnosis is usually made by the blood eosinophilia and evidences of pulmonary infiltration. It is most frequently confused with tuberculosis which, it has been pointed out, may be confused with coccidioidomycosis and other forms of atypical pneumonitis The course is benign, and the outlook excellent in most of these patients

A search for evidence of parasitic infestations should be made in all cases, and treatment governed accordingly

Kuroya and Ishida (1953) isolated an agent from an epidemic of pneumonitis in newborn children in Sendai, Japan. The virus was capable of growing in embryonated eggs and produced a hemagglutination typical of the influenza viruses. This virus upon further study appears to be closely related to influenza and has actually been designated type D influenza (*Myxovirus*, para-influenza, type 1).

Dingle and Feller (1956) state that, when specifically identified, atypical pneumonia may be diagnosed in terms of causation and excluded from the group of unknown etiology. They conclude that recent etiologic studies have provided support for the hypothesis that more than one unidentified agent may produce the syndrome of "primary atypical pneumonia of unknown etiology" and that the same agent or agents may induce both a pneumonic and a nonpneumonic form of disease

GIANT CELL PNEUMONIA

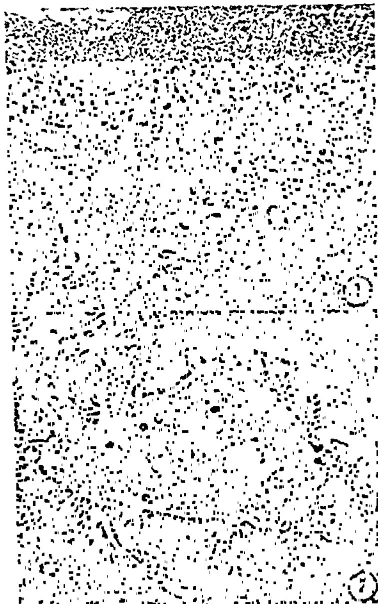
Giant cell pneumonia has been recognized primarily in infants and children and is characterized clinically by pulmonary symptoms and signs, and pathologically by the presence of multinucleated giant cells, many of which contain characteristic cytoplasmic inclusion bodies In some instances intranuclear inclusion bodies may also occur in the same giant cells, depending on the etiologic factor The characteristic pathologic picture was first described by Kromayer in 1889 in infants dying following measles and whooping cough In 1910 Hecht reported a large series of infants with giant cell pneumonia, many of the fatalities were associated with regular measles (rubeola) Inclusion bodies were pointed out by Denton in 1925 and later by Pinkerton, Smiley, and Anderson in 1945, who demonstrated cytoplasmic and intranuclear inclusion bodies in the giant cells of measles pneumonia. They

also called attention to the similar changes caused by distemper virus and at the time suggested a possible relationship between these two diseases. In 1956 this writer and co-workers reported clinicopathologic and experimental studies on giant cell pneumonia and reviewed the details of four patients, two of whom died following measles and two other children who died from pneumonitis apparently not related to typical measles. Figure 16 depicts typical examples of giant cell pneumonia showing giant cells in bronchioles with a mononuclear cellular reaction.

MacCarthy, Mitus, Cheatham, and Peebles (1958) reported the isolation of measles virus from three patients who had giant cell pneumonia with intranuclear and cytoplasmic inclusion bodies. The diagnoses of these three children were mucoviscidosis, leukemia, and Letterer-Siwe disease. None of these children exhibited a rash or had any other signs of measles during their illness. None gave a history of having had measles previously. The experimental production of giant cells in lymph tissues was accomplished by Gordon and Knighton in three of four monkeys in Bombay in 1941. Corbett in 1945 reviewed the distribution of giant cells in various body tissues and called attention to the specific nature of the Warthin-Finkeldey cell, which may be found in tonsillar and pharyngeal tissues in smears made on patients prior to the onset of rash. Enders and Peebles (1954) demonstrated characteristic giant cell formation in tissue cultures with human strains of measles virus. The photomicrographs of Figure 16 illustrate giant cell pneumonia (1) and

---

Figure 16. Two photomicrographs from different children showing the classic histopathology of giant cell pneumonia. Giant cells are shown in the lumina of the bronchi with a predominant mononuclear inflammatory reaction in the exudate and in the peribronchial areas. (From Adams, J. M., and Imagawa, D. T. (1956): Giant cell pneumonia, clinicopathologic and experimental studies. *Pediatrics* 18:888.)



Warthin-Finkeldey cells (2); tissue culture preparations showing giant cell formation are shown in Figure 2, Chapter One. Stains such as the picro-Mallory have been used to bring out inclusion bodies. Details of the staining procedure are given in Appendix A.

Several reports in the literature (1913, 1930, 1939, 1952) call attention to giant cell pathology in association with chronic pneumonic disease in children, the etiology of which has been obscure. The formation of giant cells would appear to be related to the duration of the pneumonia as many of the recorded cases survived several weeks of illness before death. In an epidemic of primary pneumonitis in infants referred to previously in Chapter Seven, giant cells were found in approximately one-third of the patients. However, the majority of the deaths occurred in less than one week, and no giant cells were found in patients who died suddenly and unexpectedly.

In experimental studies on animals inoculated with distemper virus no giant cells could be found prior to the thirteenth day following inoculation. Both giant cells and inclusion bodies were found readily from the thirteenth day on The importance of the time factor is also indicated by tissue culture studies. We were able to conclude from our clinical and experimental studies that giant cell formation with or without inclusion bodies may occur as a result of infection by several different viruses

Tzanck (1948), Blank and associates (1951), and Weller (1953) demonstrated giant cell formation by herpes simplex, herpes zoster, and varicella viruses. Giant cell formation occurs in tissue cultures that have been inoculated with *adenoviruses* These viruses may also produce distinct intranuclear inclusion bodies Giant cell production in the lung would appear to be a rather general viral phenomenon not peculiar to any one virus

INTERSTITIAL PLASMA CELL PNEUMONIA

This pneumonic process, which is largely confined to infants from one to six months of age, particularly those which have been prematurely born, will be discussed very briefly. There is an apparent geographic distribution as most of these cases have been reported from central and northern European countries, although rare instances now have been discovered in the Western Hemisphere. The etiologic factor is considered by many to be the parasite *Pneumocystis carinii.* Gadjusek (1957) reviewed the world literature and presented evidence for the parasitic etiology of this disease. The pulmonary infiltration as seen microscopically is characterized by mononuclear cells which have been classified as plasma cells, histiocytes, and possibly intermediate forms, depending in part on the histologist and stains which he employed The lungs appear typically pale gray and bluish-white with a consolidated appearance.

The clinical picture is one of insidious onset, often preceded by mild respiratory symptoms or diarrhea A long incubation period is characteristic, extending from two to five weeks Loss of weight and appetite with marked apathy characterized the symptom picture prior to the onset of increased respiratory rate Hyperpnea is a typical feature with rates from 50 to 100 per minute Cough and fever may be inconspicuous in most of these patients On physical examination widely scattered fine rales are common with evidence of increased aeration and scattered infiltrative areas as seen roentgenologically

The fatality rate at the present time is considered to be high, as most of the cases have been diagnosed at autopsy No specific therapy is recognized for these patients with plasma cell pneumonia

SUDDEN AND UNEXPECTED DEATH IN INFANCY

This clinical diagnosis refers to deaths in infants in whom there was no real sign of illness prior to death or if an illness was present it was so mild that there was never occasion for alarm and therefore the term "unexpected" is used along with "sudden death." There are many known causes of sudden death in infancy, and these are listed only, as they do not apply directly to the problem at hand. Asphyxia, hemorrhage, congenital malformations, particularly of the heart, various forms of suffocation, poisoning, and acute infection may all be causal factors. It is the acute infections with which we are primarily concerned here, as the great bulk of the evidence in the literature points directly to the respiratory passages as the primary site of disease in these babies who are often *found dead unexpectedly in their cribs.*

The condition spoken of as status thymolymphaticus referred to enlargement of thymus and lymphoid tissues which were thought to obstruct breathing and produce sudden death in infancy. This theory was never established and is no longer held by clinicians or pathologists since careful postmortem studies failed to reveal pathologic lesions consistent with this diagnosis

At the Conference on Sudden Death in Infants held in 1949 it was pointed out that in the United States a large number of babies under one year of age die of what is classified as "accidental mechanical suffocation" This diagnosis was given in 1947 for 1663 infants, with an additional 929 under one year of age attributed to thymus pathology Another large group of over 4000 are classified among the unknown causes and may well include many of the babies about whom we are at present concerned. A rather characteristic age group is typical of these patients; the curve rises sharply after one month, reaching its peak at about two months, and

dropping thereafter to almost negligible figures by one year of age.

The history is frequently a simple one: A previously well baby, usually between the ages of two and five months who may have had a recent mild cold, is suddenly discovered by the family to be dead in its crib. In the excitement of finding the baby dead, the immediate circumstances are often not carefully observed, and the first impulse is to consider that the baby might have smothered. Unless a thorough autopsy is performed, this may be the conclusion of the coroner, and the cause of death frequently is recorded as accidental mechanical suffocation Bain (1950) comments:

> The story does not end here. The parents develop a great sense of guilt which can disturb their own lives for years. Sometimes accusations of one parent about the carelessness of the other lead to quarrels and break-up of the home. Occasionally authorities, friends or neighbors may imply intentional neglect or even homicide. The social and emotional repercussions of such an "accident" are therefore widespread and of great importance

Great reliance has been placed on the pathologist and his findings in the search for the possible cause of death in these babies Werne and Garrow (1947) pointed out that in about one-quarter of the patients the etiologic reasons for the death may be found by the pathologist These include congenital cardiac disease, idiopathic cardiac enlargement, overwhelming pneumonia, meningitis, mastoiditis, and other such causes However, the great majority remain unexplained by pathologic findings.

Werne and Garrow (1947) and Davison (1945) reported large series of babies carefully studied in which evidence for infection involving the respiratory passages was the most common finding At the conference in 1949 Werne stated

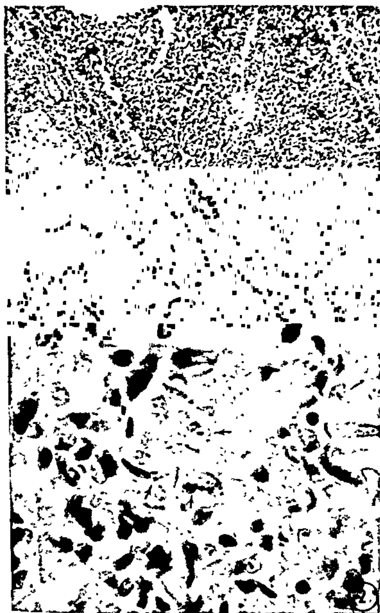
Pulmonary congestion is almost invariable and when extreme is often associated with extensive pleural hemorrhage. Pulmonary edema in varying degrees is always seen and congestion and edema often result in the presence of blood-tinged fluid in the tracheo-bronchial tree. Microscopically the most conspicuous feature of lung sections is their diminished air content as a result of vascular engorgement and infiltration with mononuclear cells, atelectasis and intra-alveolar hemorrhage, edema and alveolar cell accumulation.

Garrow and Werne (1953) very carefully point out that signs of strangulation are *not* present in these babies who have allegedly died from smothering or suffocation. They state *that the viscera and particularly the lungs are relatively pale* in true asphyxia as contrasted to the extreme pulmonary and visceral congestion observed in babies found dead in their cribs Petechiae are inconspicuous in infants with genuine asphyxial death and vary in infants who were thought to have smothered. They state that microscopic sections of the lungs in genuine acute asphyxia are virtually normal in contrast to the changes seen in infants found dead of what is believed to be a fulminating infection.

In 1943, this writer reported three cases of sudden death of infants due to pneumonia, diffuse hemorrhagic congestion of the lungs was the most striking finding. Mononuclear cell infiltration found peribronchially was evident in all cases, and the exudate in the bronchial tree contained many epithelial cells, mononuclear cells, and virtually no evidence of polymorphonuclear leukocytes or bacteria The photomicrograph (see Fig. 17 [1]) illustrates one of the small bronchioles with

---

Figure 17. Photomicrographs from a baby who was found unexpectedly dead in its crib The upper picture (1) shows a bronchiole filled with cellular debris, peribronchial and alveolar infiltration with mononuclear cells and edema In the lower picture (2), the exudate in the small bronchiole is shown with small cytoplasmic inclusion bodies in epithelial cells indicated by the arrows



peribronchial infiltrations and obvious signs of hemorrhage and edema. It was pointed out that the pathologic pulmonary reaction was similar to that reported in experimental virus pneumonia and to the pathologic picture described in infants dying of an acute respiratory pneumonitis in whom cytoplasmic inclusion bodies were found. None was found in these three infants, and it was presumed that they may have died too soon for the formation of inclusion bodies.

Recently our attention has been directed to the sudden and unexpected death of a 10-month-old infant in whom the pathologic findings were similar to those just previously outlined However, with special stains such as the picro-Mallory, we have been able for the first time to find characteristic cytoplasmic inclusion bodies in a patient with this syndrome These are shown in the photomicrograph, Figure 17 (2).

It is of interest to speculate further as to the possible causes of death in babies found dead in their cribs A combination of several factors might be involved, and the characteristic age group leads one, first of all, to postulate that immunity or lack of immunity may be an important factor in the apparent susceptibility of these babies to infection. Passive antibodies are rapidly lost in the first few weeks and months of life, and it has been postulated that these babies may be agammaglobulinemic. However, blood globulin studies have failed to reveal this possible relationship. Properdin levels have also been determined on these patients and found to be normal There are, however, many acute primary respiratory diseases in which antibodies may be minimal or lacking in these babies

The characteristic age group further would suggest the possibility of immature development on the part of the pulmonary system The baby's lung is small at birth and grows like his hand from a tiny structure to a large one The infant lung has small bronchioles, and the problem of passage of air may become a very real one, particularly in the presence

of an acute obstruction produced by infection. As pointed out many years ago, the first signs of virus pathology may be edema and congestion of tissues which lead to a sharp reduction in the size of the small bronchiolar system of infants. Poiseuille's law states that the velocity of the flow in a tube is proportional to the cross-sectional area of the tube, which means that if the diameter is reduced by a half, the velocity of flow is decreased sixteenfold. It would seem possible from the fundamental laws of physics that the effort required to ventilate tubes that are sharply reduced in diameter might very quickly become excessive and rapidly lead to hypoxic hypoxia and death. A great deal of study in the past to discover possible infectious agents, such as bacteria or viruses, has been carried out with extremely disappointing results However, new methods for virus isolation may soon be rewarding in this most difficult and complex problem

Stowens (1957), in writing about the problem of sudden unexpected death in infancy, reported on 200 deaths which were discovered in a series of 5000 pediatric deaths, or approximately 4 per cent of the total He states that 148 or 16.3 per cent of the deaths were sudden and unexpected, making this the third commonest cause in the age group one to five months Acute infection accounted for 44 per cent and congenital malformations 26 per cent. In the selection of cases he included only infants who were ostensibly well until the last moment they were seen alive He states further that specifically omitted from the study were those cases in which there was a history of "sniffles" or "loose bowels," since such minor symptoms are precursors of many infectious diseases which may run a fulminant course He proposed the hypothesis that death in these patients is the result of a generalized neurospasm mediated through the autonomic nervous system In his summary, however, the statement appears that "only the lungs show any alteration from the normal. the

changes consisting of generalized overexpansion of the alveoli and pulmonary edema. No inflammation was found."

REFERENCES

Adams, J. M. (1941): Primary virus pneumonitis with cytoplasmic inclusion bodies; study of an epidemic involving thirty-two infants with nine deaths, *J.A.M.A.*, **116**:925

Adams, J M. (1943). Sudden death in infants due to pneumonia, *J. Pediat.*, **23** 189.

Adams, J M (1953): Comparative study of canine distemper and a respiratory tract disease of man, *Pediatrics*, **11**:15

Adams, J. M.; Imagawa, D T; Yoshimori, M; and Huntington, R W (1956). Giant cell pneumonia: Clinicopathologic and experimental studies, *Pediatrics*, **18**:888.

Arey, J B, and Sotos, J (1956). Unexpected death in early life, *J Pediat*, **49** 523.

Bain, K (1950) When a baby dies unexpectedly, *The Child*, **14** 130.

Blank, H; Burgson, C F; Baldridge, G D, McCarthy, P L, and Urbach, F (1951). Cytologic smears in diagnosis of herpes simplex, herpes zoster, and varicella, *J A M.A*, **146** 1410

Chown, B (1939) Giant cell pneumonia of infancy as a manifestation of vitamin A deficiency, *Am J Dis Child*, **57** 489

Commission on Acute Respiratory Diseases (1944) Epidemiology of atypical pneumonia and acute respiratory disease at Fort Bragg, N C, *Am J Pub Health*, **34** 335

Commission on Acute Respiratory Diseases (1945) Experimental attempt to transmit primary atypical pneumonia in human volunteers, *J Clin Invest*, **24** 175

Commission on Acute Respiratory Diseases (1946) The transmission of primary atypical pneumonia to human volunteers, *Bull Johns Hopkins Hosp*, **79** 97

Commission on Acute Respiratory Diseases (1947) Experimental transmission of minor respiratory illness to human volunteers by filter-passing agents I Demonstration of two

types of illness characterized by long and short incubation periods and different clinical features, *J. Clin. Invest*, **26**:957
Commission on Acute Respiratory Diseases (1947): Experimental transmission of minor respiratory illness to human volunteers by filter-passing agents II Immunity on reinoculation with agents from two types of minor respiratory illness and from primary atypical pneumonia, *J. Clin Invest.*, **26** 974
Conference on Sudden Death in Infants (1949), Public Health Service (unpublished)
Corbett, E U. (1945). The visceral lesions in measles, with report of Koplik's spots in colon, *Am J Path*, **21** 905
Davison, W H. (1945): Accidental infant suffocation, *Brit M. J*, **2** 251.
Denton, J (1925). Pathology of fatal measles, *Am J M. Sc.*, **169** 531
Dingle, J H, *et al* (1944) Primary atypical pneumonia, etiology unknown I, II, III, *Am J Hyg*, **39** 67, 197, and 269
Dingle, J H, and Feller, A E (1956) Noninfluenzal viral infections of the respiratory tract, *New England J. Med*, **254** 465
Eaton, M D (1950). Action of aureomycin and chloromycetin on virus of primary atypical pneumonia, *Proc Soc Exper Biol & Med*, **73** 24
Eaton, M D, Meiklejohn, G, and van Herick, W (1944) Studies on etiology of primary atypical pneumonia filterable agent transmissible to cotton rats, hamsters, and chick embryos, *J Exper Med*, **79** 649
Enders, J F, and Peebles, T C (1954) Propagation in tissue cultures of cytopathogenic agents from patients with measles, *Proc Soc Exper Biol & Med*, **86** 277
Farber, S (1934) Fulminating streptococcus infections in infancy as cause of sudden death, *New England J Med*, **211** 154
Feller, A E (1948) Primary atypical pneumonia In *Diagnostic Procedures for Virus and Rickettsial Diseases* American Public Health Association, New York, 347 pp

Finkeldey, W. (1931): Uber Riesenzellbefunde in den Gaumenmandeln, Zugleich ein Beitrag zur Histopathologie der Mandelveränderungen im Maserninkubationstadium, *Arch. path Anat.*, **281**:323.

Finland, M.; Jolliffe, L. S.; and Parker, F. (1948): Pneumonia and erythema multiforme exudativum, *Am. J. Med*, **4**:473

Gajdusek, D. C. (1957): Pneumocystis carinii—etiologic agent of interstitial plasma cell pneumonia of premature and young infants, *Pediatrics*, **19**:543.

Garrow, I., and Werne, J. (1953): Sudden apparently unexplained death during infancy III. Pathological findings in infants dying immediately after violence, contrasted with those after sudden apparently unexplained death, *Am. J. Path*, **29**:833.

Ginsberg, H. S.; Badger, G F.; Dingle, J. H.; Jordan, W. S, Jr; and Katz, S. (1955). Etiologic relationship of RI-67 agent to "acute respiratory disease" (ARD), *J. Clin. Invest*, **34**: 820.

Gordon, H, and Knighton (1941) Experimental measles, lymphoid tissues of animals inoculated with the virus of human measles, *Am. J. Path*, **17** 165.

Hecht, V (1910) Die Riesenzellenpneumonie im Kindesalter, eine historichexperimentelle Studie, *Beitr. path Anat*, **48** 263

Hilleman, M R; Werner, J H, Adair, C V, and Dreisbach, A R (1955). Outbreak of acute respiratory illness caused by RI-67 and influenza A viruses, Fort Leonard Wood, 1952–1953, *Am J Hyg*, **61** 163

Hilleman, M R; Werner, J H, Dascomb, H E, Butler, R L, and Stewart M T (1955) Epidemiology of RI (RI-67) group respiratory virus infections in recruit populations, *Am. J. Hyg*, **62** 29

Horsfall, F L, Jr (1948) Diagnosis of primary atypical pneumonia In *Diagnosis of Viral and Rickettsial Infections*, symposium held at the New York Academy of Medicine

Horsfall, F L, Jr, Curnen, E C, Mirick, G S, Thomas, L, and Ziegler, J E. (1943) A virus recovered from patients with primary atypical pneumonia, *Science*, **87** 289

Karsner, H. T., and Meyers, A. E. (1913) Giant cell pneumonia, *Arch Int. Med.*, **11**.534

Keefer, C. S., and Hewitt, W L (1955): Pulmonary infections, the pneumonias. In Pullen, R. L (ed.) *Pulmonary Diseases.* Lea & Febiger, Philadelphia

Kromayer, E (1889): Über die sogenannte Katarrhalpneumonie nach Masern und Keuchhusten, *Arch, path Anat*, **117**: 452

Krugman, S; Goodrich, C H; and Ward, R (1957) Primary varicella pneumonia, *New England J Med*, **257**.843

Kuroya, M, and Ishida, W (1953) Newborn virus pneumonitis (type Sendai), *J Immunol*, **75** 71

MacCarthy, K, Mitus, A, Cheatham, W, and Peebles, T (1958) Isolation of virus of measles from 3 fatal cases of giant cell pneumonia, *Proc. Soc. Ped Res*, 28th Annual Meeting, May 6, p 56

Meiklejohn, G, Thalman, W G, Waligora, D J, Kempe, C H, and Lennette, E H (1954) Chemotherapy of primary atypical pneumonia, *J A M A*, **154** 553

Moore, R A, and Gross, P (1930) Giant cells in inflammation of the lung in children, *Am J Dis Child*, **40** 247

Owen, C A (1944) Primary atypical pneumonia, *Arch Int Med*, **73**·217

Pinkerton, H, Smiley, W L, and Anderson, W A D (1945) Giant cell pneumonia with inclusions A lesion common to Hecht's disease, distemper and measles, *Am J Path*, **21** 1

Pullen, R L (1950) *Communicable Diseases* Lea & Febiger, Philadelphia

Reimann, H A (1938) An acute infection of the respiratory tract with atypical pneumonia, *J A M A*, **3** 2377

Reimann, H A (1947) The viral pneumonias and pneumonias of probable viral origin, *Medicine*, **26** 167

Reimann, H A (1954) *Pneumonia* Charles C Thomas, Publisher, Springfield, Ill

Scadding, J G (1937) Lung changes in influenza, *Quart J. Med*, **6** 425

Scott, R F, Thomas, W A, and Kissane, J M (1959) Rheumatic pneumonitis Pathologic features, *J Pediat*, **54** 60

Shope, R. E. (1936): Influenzas of swine and man, *Medicine*, **15**:453.

Smadel, J. E; Green, R. H.; Paltauf, R. M.; and Gonzales, T. A (1942): Lymphocytic choriomeningitis; two human fatalities following an unusual febrile illness, *Proc. Soc. Exper. Biol & Med*, **49**:683.

Stokes, J; Kenny, A. S; and Shaw, D. R. (1939): A new filterable agent associated with respiratory infections, *Tr. & Stud Coll. Physicians Philadelphia*, **6**:329.

Stowens, D. (1957): Sudden unexpected death in infancy, *Am. J. Dis. Child.*, **94**:674.

Stuart-Harris, C. H (1945): Influenza epidemics and the influenza viruses, *Brit. M. J.*, **1**:209.

Tzanck, A (1948): Le cyto-diagnostic immédiat en dermatologie, *Ann. dermat. et syph.*, **8** 205.

Von Meyenburg, H. (1942): Eosinophilic pulmonary infiltration, *Schweiz. med. Wchnschr.*, **72**:809 Abstract (1943): *J.A.M.A.*, **121**:626.

Warthin, A S (1931): Occurrence of numerous large giant cells in the tonsils and pharyngeal mucosa in the prodromal stage of measles; report of 4 cases, *Arch. Path*, **11**:864

Watson, E A, and Plummer, P. J G (1942) Distemper inclusion bodies, *Am. J. Vet. Res*, **3**:350

Weir, J M, and Horsfall, F. L., Jr. (1940) Recovery from patients with acute pneumonitis of a virus causing pneumonia in the mongoose, *J. Exper. Med.*, **72** 595

Weller, R W (1952). Giant cell pneumonia with inclusions, *Pediatrics*, **10** 681

Weller, T H (1953). Serial propagation in vitro of agents producing inclusion bodies derived from varicella and herpes zoster, *Proc Soc Exper Biol & Med.*, **83** 340

Werne, J and Garrow, I (1947) Sudden deaths of infants allegedly due to mechanical suffocation, *Am J Pub Health*, **37** 675

Wolman, M, Izak, G, Freund, E, and Shamir Z (1952): Studies on interstitial giant cell pneumonia report of 5 cases with autopsy, *Am J. Dis Child*, **83** 573

Chapter Ten

Q FEVER, PSITTACOSIS, AND LEPTOSPIROSIS

Q FEVER

Q fever is an acute febrile disease which must be considered in the differential diagnosis of any influenza-like illness. The disease is characterized by sudden onset of fever with general malaise, muscular aching, and severe headache. Cough occurs in a certain percentage of patients, and there are few physical findings of pulmonary disease, most of the changes being discovered by roentgenography of the chest. Unlike other rickettsial diseases, Q fever produces no rash and fails to show agglutinins with the proteus organisms in the Weil-Felix reaction. The organism responsible for this respiratory disease is *Coxiella burneti* which may be isolated from patients by animal inoculation with the blood of sick individuals. Diagnosis can further be established by the demonstration of a rising titer by complement-fixation or rickettsial agglutinating antibodies early in the course of convalescence. The agglutination test is considered to be superior to the complement-fixation test by several workers as it becomes positive earlier in the course of disease. Complement-

fixing antibodies appear during the second week of illness and reach their peak by the end of the third week.

Clinical Features

Most of the clinical studies have been made on military personnel and several of these stem from Italy as a result of epidemics among military personnel stationed there during World War II. An incubation period of from 14 to 26 days with an average of 19 days is customary, followed by rapid onset of headache and feverishness, with loss of appetite. Early in the illness, respiratory symptoms are not common, and fever and headache may be the most prominent symptoms. The incubation period may occasionally be brief—from 1 to 10 days. The majority of patients have fever for three to six days. Mild dry coughs develop in most of the patients; many complain of pain in the chest, at which time physical examination may reveal abnormal breath sounds and dullness. Evidence of pulmonary involvement can be demonstrated most readily by means of roentgenograms of the chest, and these are positive in the great majority of patients with Q fever. Even the mildly ill will often show evidences of pulmonary infiltration with localized shadows being somewhat characteristic of the illness. The shadows are often homogeneous and have a ground-glass appearance. The "snowball" shadow has been said to be characteristic of the infiltration as demonstrated on the x-ray film of the chest.

There are few diagnostic aids since the white blood count and differential count are essentially normal with slight increases in the erythrocyte sedimentation rate. During the early stages of the patient's illness the differential diagnosis may involve any of the influenza-like diseases. The pulmonary findings develop late in the first week at which time the differential diagnosis includes the bacterial pneumonias, primary atypical pneumonia, psittacosis, and other diseases such as

coccidioidomycosis and tuberculosis. The organism may be isolated without difficulty from the blood of patients. Several laboratory animals, such as guinea pigs, mice, and monkeys, and embryonated eggs have been employed in isolation studies. The organisms may be identified from the microscopic examination of splenic smears stained by Giemsa's or Machiavello's method.* Complement-fixing antibody tests are the most practical and safest method for establishing the diagnosis of Q fever. Titers 1 to 8 and 1 to 20 are considered significant, but as a rule convalescent titers will be much higher, often in the range of 1 to 160 There are no cross-reactions with other members of the rickettsial group, psittacosis, influenza viruses, or cold agglutinins.

Epidemiologically, the disease for the most part has been essentially occupational, being limited almost entirely to laboratory personnel and workers in slaughterhouses. Derrick (1944) studied the natural history of the disease in Australia where he demonstrated its transmission in nature by ticks He also described a mild disease in cattle Slaughterhouse workers may contract the disease by direct contact or by inhalation of dust from hides contaminated by tick feces Certain common tick species in several regions of the United States are naturally infected with the organisms of Q fever Davis and Cox (1938) demonstrated that *Dermacentor andersoni* ticks are capable of transmitting the disease to guinea pigs by feeding.

Monagahan and Brueckmann (1958) reported an epidemic from Leghorn, Italy, involving 49 individuals at the U S Army installation They concluded that the disease was transmitted by the inhalation of infected dust from animals on nearby farms Sigel and associates (1950) reported Q fever in a wool and hair processing plant in Philadelphia The epidemic occurred in the first three months of the year and in-

* See Appendix A for staining method

volved approximately 30 employees of the plant. They state that the disease was characterized by an acute respiratory illness which was generally referred to as the "flu" or "grippe." The clinical spectrum of illness was revealed by study of the blood of employees which showed that 67 of the individuals had positive reactions against Q fever.

Monagahan and Brueckmann (1958) reported that antibiotic therapy proved successful in treating Q fever. Oxytetracycline was the most effective of several antibiotics tried and was used extensively in their series. Doses of 1 to 2 gm were given daily in divided doses with favorable clinical responses occurring in about 45 hours. The average length of treatment required in their series was 4.4 days. Penicillin did not appear to alter the course of disease. No other therapy is effective, but general supportive and symptomatic measures may be very helpful. No relapses occurred following therapy, and they state that convalescence was about what could be expected in any influenza-like illness.

PSITTACOSIS

This disease, commonly referred to as psittacosis because of its early recognition in psittacine birds, is an acute infectious disease of many different species of birds and is communicable to man at all ages. As a rule, it is a mild or inapparent infection but may result in severe illness with a high mortality. The infective agent belongs to the lymphogranuloma venereum group of agents which are intermediate between the rickettsiae and viruses. The etiologic agent is coccoid elementary bodies known as *Miyagawanella psittaci*. This group of agents has been isolated from the respiratory passages of healthy and diseased mammals, and it is now apparent that a person-to-person communicability exists. These agents may be nonavian and responsible for direct human disease

The earliest descriptions of this influenza-like disease which can be directly attributable to sick birds was recorded by Ritter in 1880; however, it was not until about 1930 that interest throughout the world was stimulated by the demonstration of human cases that were discovered in more than a dozen different countries. At that time, South American parrots were shown to be the primary source of infection. Levinthal, Coles, and Lillie (1930) almost simultaneously discovered the coccoid bodies, and their etiologic relationship was pointed out by Bedson and Bland in 1932. The disease was induced in monkeys by Rivers and Berry (1931), and a mouse test was devised for isolation of virus from sputum of patients. Hilleman in 1945 demonstrated the antigenic relationship of certain avian and nonavian strains. Psittacosis is widely distributed in birds, and it is now apparent that healthy fowl will harbor the organisms and shed infectious agents Meyer (1942) states that enzootic psittacosis is constantly present in parakeet aviaries as well as in pigeon- and duck-breeding establishments.

There are now over a hundred infections that have been attributed to pigeons, ducks, and chickens Winter epidemics of the disease predominate, but cases have been known to occur throughout the year. A higher incidence is recorded in women who tend to be bird fanciers and engage in breeding of birds. Transmission occurs by air, handling of sick or dead birds, or by the excreta from such birds which may be actively or latently infected, and by wounds created by bites. The disease has been transmitted from person to person; the respiratory passages are considered the main portal of entry. An epidemic in Louisiana in 1943 produced eight deaths and 19 recognized infections among nursing attendants. During the 10-year period from 1940 to 1949, 77 cases with seven deaths were recorded in California However, federal and

state control measures have resulted in diminishing the spread of infection, and because of these excellent control measures the disease is now rarely diagnosed in California.

Pulmonary changes in man and monkey are distinguished by patchy consolidations which appear microscopically as cellular infiltration of the aveolar walls and proliferative changes in the lining cells of the aveoli. In the fully developed lesions, the exudate reveals many desquamated epithelial and phagocytic cells with characteristic cytoplasmic elementary bodies. Hepatic cells reveal focal necrosis and contain typical elementary bodies of psittacosis. The spleen may be enlarged and engorged; hemorrhagic thrombi may be found in the adrenal glands. Congestion and edema of brain tissue have been described with capillaries showing proliferative and degenerative changes.

Clinical Features

A history of exposure to sick birds is helpful but not necessary when considering the etiology of acute respiratory disease. The onset of disease is abrupt with anorexia, sore throat, headache, backache, photophobia, and chills as the principal symptoms. As in Q fever, a nonproductive cough may develop in a few days, and fever may continue to be elevated into the second or third week of illness. The pulse in psittacosis, as in typhoid fever, may be relatively slow with mild increases in respiratory rate. The physical signs are those of consolidation, which tends to shift and spread from one area to another. Physical findings are often scanty as compared with the densities seen in the scout film of the chest. The incubation period varies between 7 and 15 days.

In patients with typhoidal symptoms and relatively slow pulse and respiratory rates, psittacosis should be seriously considered. The white count may be normal or low. Influenza and atypical pneumonia due to other viral agents should be

considered as well as Q fever. The complement-fixation test becomes positive by the end of the first week and is very helpful in the diagnosis of this disease. Mice inoculated with blood and sputum from patients may demonstrate the etiologic agent. Intracytoplasmic elementary bodies may be stained with Machiavello's method * and appear bright red while the cellular elements take the pale blue-green stain, thus sharply revealing the typical virus bodies of psittacosis.

Psittacosis may occur at all ages but is relatively rare in children. Armstrong (1930) recorded 169 patients of whom only eight were under 14 years of age. A less intense exposure may account for the rare or mild forms of the disease which occur in childhood. In the treatment of this disease, antibiotics have been lifesaving in a disease which carried a relatively high fatality rate prior to their use. Meyer and Eddie (1947) reported 21 fatal infections among 228 patients between 1940 and 1946, most of the deaths occurring in older age groups. Meiklejohn and co-workers (1946) stated that sulfadiazine was effective against two of the classic strains of psittacosis, and Heilman and Herrell (1944) demonstrated clearly the beneficial effects of penicillin in experimental disease. Dosage should be determined in accordance with the severity of infection in each patient and continued according to the clinical judgment of the physician. The rigorous segregation of patients with psittacosis is highly recommended because viral agents have been isolated into the third week of illness. Discharges should be disposed of according to the best techniques. A search for the source of infection should be made and all cases should be reported. As Meyer and others have shown, healthy birds may harbor the virus and shed the infective agent and upon removal to unhealthy surroundings they may develop fatal disease. The entire spectrum of illness from latent to severe disease may exist in birds. From an epidemio-

* See Appendix A for staining method.

logic standpoint, apparently healthy birds are frequently of greater importance than visibly sick birds.

LEPTOSPIROSIS

This disease may manifest itself primarily with fever and suffusion of the conjunctiva. In its mild forms it is frequently confused with common respiratory diseases due to many other causes. The common types of leptospira are *Leptospira icterohaemorrhagiae*, transmitted by rats, *L. canicola*, transmitted by dogs, and *L. pomona*, found in cattle and swine. Ingestion of contaminated materials, food, and water may cause disease in humans, with an incubation period of one to two weeks. Clinical features include the common symptoms and signs of headache, vomiting, and muscular aches with suffusion of the conjunctiva. Jaundice may be present in less than 10 per cent of the patients and is not a striking or reliable sign. Albuminuria, however, is a common finding and may be most helpful in pointing the way to the correct diagnosis. The kidneys, liver, muscle, conjunctiva, and meninges are the main sites of inflammation.

Spirochetes are readily cultured from one drop of blood, and the diagnosis may be confirmed by the appearance of specific antibodies; agglutination and complement-fixation tests are available in many laboratories. No specific treatment is known.

REFERENCES

Andrewes, C H, and Mills, K C (1943) Psittacosis (ornithosis) virus in English pigeons, *Lancet*, 1 292

Armstrong, C. (1930) Psittacosis; epidemiological considerations with reference to 1929–30 outbreak in United States, *Pub Health Rep*, 45 2013

Ashe, W F, Pratt-Thomas, H R, and Kumpe, C W (1941) Weil's disease, complete review of American literature and abstract of world literature, *Medicine*, 20 145

Bedson, S. P. (1932): Nature of elementary bodies in psittacosis, *Brit. J. Exper. Path*, 13:65.

Bedson, S. P. (1933): Immunological studies with virus of psittacosis, *Brit. J. Exper. Path.*, 14:162.

Bedson, S. P., and Bland, J. O. W. (1932): Morphological study of psittacosis virus, with description of developmental cycle, *Brit. J. Exper. Path.*, 13:461.

Bengtson, I. A. (1941): Immunological relationships between the rickettsiae of Australia and American "Q" fever, *Pub. Health Rep.*, 56:272.

Burnet, F. M., and Freeman, M. (1937): Experimental studies on the virus of "Q" fever, *M. J. Australia*, 2:299.

Burnet, F. M., and Rountree, P. M. (1935). Psittacosis in developing egg, *J. Path. & Bact*, 40:471.

Buzzard, E. M., and Wylie, J. A. H. (1947): Meningitis leptospira, *Lancet*, 2:417.

Clark, W. H., and Lennette, E. H. (1952): Treatment of Q fever with antibiotics, *Ann New York Acad Sc*, 55:1004.

Coles, A C (1930). Micro-organisms in psittacosis, *Lancet*, 1 1011.

Commission on Acute Respiratory Diseases (1946): A laboratory outbreak of Q fever caused by the Balkan grippe strain of *Rickettsia burneti*, *Am J. Hyg.*, 44:88

Commission on Acute Respiratory Diseases (1946) Epidemics of Q fever among troops returning from Italy in the spring of 1945 II Epidemiological studies, *Am J. Hyg*, 44 88

Commission on Acute Respiratory Diseases (1946) Identification and characteristics of the Balkan grippe strain of *Rickettsia burneti*, *Am J Hyg.*, 44:110

Cox, H R (1939). Studies of a filter-passing infectious agent isolated from ticks V Further attempts to cultivate in cell-free media Suggested classification, *Pub Health Rep*, 54: 1822

Davis, G E, and Cox, H R (1938). A filter-passing infectious agent isolated from ticks I. Isolation from *Dermacentor andersoni*, reactions in animals, and filtration experiments, *Pub Health Rep.*, 53 2259.

Derrick, E. H. (1937): "Q" fever, a new fever entity: Clinical features, diagnosis and laboratory investigation, *M. J. Australia*, 2:281.

Derrick, E. H. (1944): The epidemiology of Q fever, *J. Hyg.*, 43:357.

Dyer, R. E.; Topping, N. H.; and Bengtson, I. A. (1940): An institutional outbreak of pneumonitis. II. Isolation and identification of causative agent, *Pub. Health Rep.*, 55:1945

Eaton, M. D.; Beck, M D; and Pearson, H E (1941): Virus from cases of atypical pneumonia, relation to viruses of meningopneumonitis and psittacosis, *J. Exper. Med.*, 73.641.

Haagen, E., and Mauer, G. (1938): Über eine auf den Menschen ubertragbare Viruskrankheit bei Sturmvogeln und ihre Beziehung zur Psittakose, *Zentralbl. Bakt.* (Abt. 1), 143:81.

Heilman, F R., and Herrell, W. E (1944): Penicillin in treatment of experimental ornithosis, *Proc. Staff Meet., Mayo Clin*, 19.57

Hilleman, M. R (1945): Immunological studies on psittacosis-lymphogranuloma group of viral agents, *J. Infect. Dis*, 76:96

Krumwiede, C; McGrath, M, and Oldenbusch, C. (1930): Etiology of the disease psittacosis, *Science*, 71:262.

Levinthal, W (1930) Die Atiologie der Psittakosis, *Klin Wchnschr*, 9 654

Lillie, R D (1930): Psittacosis, rickettsia-like inclusions in man and in experimental animals, *Pub. Health Rep*, 45.773.

Meiklejohn, G, Wagner, J C., and Beveridge, G W (1946): Studies on chemotherapy of viruses in psittacosis-lymphogranuloma group, effect of penicillin and sulfadiazine on 10 strains in chick embryos, *J. Immunol*, 54:1

Meyer, K F (1942). Ecology of psittacosis and ornithosis (De Lamar lecture). *Medicine*, 21.175

Meyer K F (1952) *Psittacosis (Ornithosis), Diseases of Poultry* Iowa State College Press, Ames, Iowa, Chapt 22

Meyer K F, and Eddie, B (1933) Latent psittacosis infections in shell parakeets, *Proc Soc Exper Biol & Med*, 30 484

Meyer K F, and Eddie, B (1939) Value of complement fixation test in diagnosis of psittacosis, *J Infect Dis* 65 225

Meyer, K. F., and Eddie, B. (1947): Knowledge of human virus infections of animal origin, *J.A.M.A.*, 133:822.

Monagahan, D. G., Jr., and Brueckmann, F. R. (1958): Outbreak of Q fever in an Army installation in Italy, *Am. J. Med.*, 24:310.

Ormsbee, R. A., and Pickens, E. G. (1955): A comparison by means of the complement-fixation test of the relative potencies of chloramphenicol, aureomycin and terramycin in experimental Q fever infection in embryonated eggs, *J. Infect. Dis.*, 96:162.

Peterson, E.; Spalding, O. B.; and Wildman, O. (1930): Psittacosis; clinical and roentgenologic study of seven cases with postmortem observations in one case, *J.A.M.A.*, 95:171.

Ritter, J. (1880). Beitrag zur Frage des Pneumotyphus. (Eine Hausepidemie in Uster [Schweitz] betreffend.), *Deutsches Arch. klin. Med.*, 25:53.

Rivers, T. M.; Benjamin, B., and Berry, G. P. (1930): Psittacosis; report of case, *J.A.M.A.*, 95:577.

Rivers, T. M., and Berry, G. P. (1931): Psittacosis, experimentally induced infections in monkeys, *J. Exper. Med.*, 54:129.

Rivers, T. M., and Berry, G. P. (1932): Laboratory method for diagnosis of psittacosis in man, *Proc. Soc. Exper. Biol. & Med.*, 29:942.

Rivers, T. M., Berry, G. P., and Sprunt, D. H. (1931): Psittacosis, experimentally induced infections in parrots, *J. Exper. Med.*, 54:91.

Robbins, F. C., and Ragan, C. A. (1946): Q fever in the Mediterranean area. Report of its occurrence in Allied troops. I. Clinical features of the disease, *Am. J. Hyg.*, 44:6.

Sigel, M. M., *Scott, T. F. McN.; Henle, W.*, and Janton, O. H. (1950). Q fever in a wool and hair processing plant, *Am. J. Pub. Health*, 40:524.

Smadel, J. E., Snyder, J. J.; and Robbins, F. C. (1948): Vaccination against Q fever, *Am. J. Hyg.*, 47:71.

Sturdee, E. L., and Scott, W. M. (1930). A disease of parrots communicable to man (psittacosis), Ministry of Health, Re-

ports on Public Health and Medical Subjects, No 61, London, His Majesty's Stationery Office.

Topping, N. H.; Shepard, C. C.; and Huebner, R J. (1946): Q fever: an immunological comparison of strains, *Am. J. Hyg.*, **44**:173.

Topping, N. H.; Shepard, C. C ; and Irons, J. V. (1947): Q fever in the United States. I. Epidemiologic studies of an outbreak among stock handlers and slaughterhouse workers, *J.A M.A.*, **133** 813.

Treuting, W. L , and Olson, B. J. (1944): Epidemic of severe pneumonitis in Bayou region of Louisiana; clinical features of disease, *Pub. Health Rep.*, **59**:1331

Wentworth, B. B. (1955): Historical review of the literature on Q fever, *Bact. Rev.*, **19**:129.

Yanamura, H. Y., and Meyer, K. F. (1941). Studies on virus of psittacosis cultivated in vitro, *J. Infect. Dis.*, **68** 1.

Chapter Eleven

STREPTOCOCCAL AND OTHER BACTERIAL INFECTIONS OF THE RESPIRATORY SYSTEM

INTRODUCTION

Attention will be directed primarily to group A streptococci as they together with the diphtheria bacilli are probably responsible for the great majority of primary throat infections due to bacteria. Many organisms are known to be transient residents of the respiratory passages but are not considered as primary invaders capable of initiating disease in the nasopharyngeal areas. The bulk of the evidence supports the idea that the pneumococcus, staphylococcus, *Hemophilus influenzae*, and meningococcus in most instances are secondary complicating infections that are preceded by a viral infection, at which time they increase in numbers and may become true invaders.

The symptomatology often relates to the secondary bacterial invader with toxemia and other complications dominating the picture. Complications such as cervical adenitis, otitis media, laryngotracheobronchitis, and pneumonia have for many years been considered either a primary infection or caused by sec-

ondary bacterial invasion. It is important to emphasize that with the advent of antibiotics and other specific antibacterial agents it is now evident that there are many nonbacterial causes of cervical adenitis and otitis media as well as lower pulmonary disease. This means that great clinical judgment is required in the use of specific drugs if one is to reserve their use mainly to infections caused by bacteria. The presence of cervical adenitis and otitis media does not necessarily indicate bacterial disease. However, they do represent extension of disease from the nasopharyngeal passage and may in themselves be strong indications for the use of antibacterial drugs

STREPTOCOCCAL INFECTIONS

The group A streptococcus is the commonest bacterium that invades the respiratory passages. Group specificity is determined by the reaction of the polysaccharide in the streptococcal organism with specific antisera. Although the majority of human infections are caused by group A streptococci, certain organisms of groups C and G may rarely infect human beings Type-specific M protein is the surface antigen of group A streptococci and is responsible for the subtypes of group A which now number more than 40, it is this same antigen that may interfere with phagocytosis and probably is primarily responsible for the invasiveness of group A streptococci Type-specific antibody against M protein is *the primary* factor in immunity to streptococcal infection Thus, man may be infected by several different types of streptococci of the group A classification, and evidence for infection by the same type in the same individual is rare indeed

Erythrogenic toxin is considered responsible for the rash in scarlet fever, but there are many antigenic extracellular substances, such as streptolysin O, streptokinase, hyaluronidase, and desoxyribonuclease, known to be elaborated by hemolytic streptococci. Therefore, it is important to establish

infection by an evaluation of antibody changes in the course of infection

Clinical Features

Streptococcal pharyngitis is characterized by sudden onset of sore throat which is accompanied by fever and constitutional symptoms such as headache and malaise The pharynx appears diffusely red with the brightness of scarlet accompanied by signs of swelling and edema The tonsils may be so swollen as to meet in the midline. The majority of patients will show small patches of white or grayish exudate on the tonsillar or pharyngeal mucosa The exudate, however, may not appear for 24 to 36 hours following the acute onset of disease. It may be pin-point in nature early in the infection, becoming confluent with a dirty gray-yellowish membrane quite easily removed by swabbing The regional cervical lymph nodes become enlarged and tender to palpation and may be responsible for signs of a stiff neck. The mucous membranes in the nasopharyngeal areas are intensely inflamed and hyperemic and occasionally lead to bleeding

The picture just presented is not typical of streptococcal disease as seen in infancy and the preschool child Powers and Boisvert (1944) have described the varying symptomatology with age and have pictured the infant's illness as being characterized by low-grade fever with anorexia, vomiting, and mucopurulent discharges from the nose with marked excoriation of the nares From six months to three years the child suffers from a more severe illness, often insidious in its onset, characterized by fever which may persist for many weeks The pharynx is only mildly inflamed, but the nasal discharge is purulent and profuse Systemic symptoms characterized by anorexia, vomiting, and loss of weight are prominent The untreated patient frequently suffers from complications such as otitis media and cervical adenitis

Scarlet fever is more common in the age group 3 to 10 years, at which time a more localized type of infection occurs. Tonsillitis and pharyngitis are the prominent physical findings, usually without exudate. The papular erythematous eruption so characteristic of scarlet fever is a most helpful diagnostic sign. Rash appears on the body and is increased in the folds, rarely involving the face as is so characteristic with the macular-papular eruption of measles. Flushing, however, is common with circumoral pallor. The papular eruption, which feels rough prior to the onset of erythema, is particularly helpful in highly pigmented individuals. An enanthem appears over the palate and is often petechial in character. The mucous membranes are intensely red and scarlet in color, and the tongue presents typical strawberry characteristics with desquamation and swollen papillae.

There are many important and serious complications associated with streptococcal infections, the great majority of which may be prevented by early and effective treatment Studies by Powers and Boisvert (1944) show a marked decrease in the incidence of suppurative complications following the introduction of specific therapy. There is also evidence that the nonsuppurative sequelae may be prevented by adequate treatment of the primary illness. The main nonsuppurative diseases are rheumatic fever and acute glomerular nephritis, which appear to be commoner in older children and adults than in the earlier age groups.

Evidence for a clinical spectrum in streptococcal infections has been presented by Rammelkamp (1955) in which he indicates that the diagnostic error as the result of culture and serologic studies has been nearly 20 per cent The common use of serologic tests now indicates that a wide spectrum exists in streptococcal infections. Proven infections in the Cleveland Family Studies amounted to about 2.5 per cent of all of the respiratory illnesses Evans (1958) has recorded as high

as 10 per cent in health service studies at the University of Wisconsin, but many of these diagnoses were based on cultural findings. In epidemics these percentages have been greatly increased. The studies reported by the Commission on Acute Respiratory Diseases during World War II showed that exudative tonsillitis was not caused by the hemolytic streptococcus in the majority of instances but was nonbacterial in nature. They were able to establish that in only about 50 per cent of the patients in whom an organism was cultured was there true evidence for invasion by the streptococcus as demonstrated by *antistreptolysin* titer rises Pharyngitis due to many other causes with exudate must be differentiated from streptococcal pharyngitis. These include infectious mononucleosis in which the membrane may appear similar to that caused by streptococci or diphtheria bacilli; herpes simplex and Vincent's angina infections may also present an exudative pharyngitis In nonbacterial exudative pharyngitis (*adenovirus* infection) a white pin-point type of rash is usually localized on the tonsils, but overlapping symptomatology such as cervical adenitis makes differential diagnosis at times extremely difficult. The white count is usually normal, and frequently no streptococci may be isolated on culture

Diagnosis

The total leukocyte count is usually elevated above 12,000 cells per milliliter with an increase in the polymorphonuclear cells. In most other conditions involved in the differential diagnosis this striking elevation is not a common accompaniment In addition to the elevated leukocyte count, a throat culture may be most helpful in arriving at an etiologic diagnosis. These cultures can be made simply and read by any physician with very little experience in the field of clinical bacteriology A prompt inoculation of the culture following the swabbing of the patient's nose and throat into infusion agar

containing 5 per cent sheep blood will usually yield excellent results. The group A streptococci produce a clear zone of hemolysis which is easily distinguished from the greenish, incomplete type of hemolysis caused by other types of streptococci on sheep blood agar. Schmidt and Rammelkamp (1957) recommend applying the culture to one side of the medium with streaking of the plate and also suggest stabbing into the agar with the loop as some hemolytic streptococci produced better hemolysis under reduced oxygen tension.

A new medium for culture of the beta hemolytic streptococcus has recently been developed by Rantz and associates (1959); it contains maltose and nucleic acid as well as some neomycin The zone of hemolysis is intensified by this medium and aids in rapid identification They also recommend the use of swabs with Dacron tips instead of cotton tips as they are less absorbent and give better results. Hollinger (1959) reported recently on the use of filter paper strips for shipping cultures to the laboratory.

It should be emphasized that the mere finding of hemolytic streptococci on throat cultures does not establish the diagnosis unequivocally *Certain hemolytic organisms of groups* C, D, and G may occasionally be found in the human pharynx, and C and G have also been found to cause pharyngitis in man The carrier state is not uncommon and may occur even in the presence of other infections Organisms have also been shown to be present for weeks and months in people who have been inadequately treated

If in doubt the pathogenic characteristics of the organism should be determined, but most important is the demonstration of increases in streptococcal antibody when early and late specimens are compared. A twofold rise in the antistreptolysin O titer is sufficient evidence to establish infection Heavy and predominant growths provide a very practical means of assuring the diagnosis, and when these are asso-

ciated with the typical syndrome little doubt should remain as to the indications for therapy. When only a few colonies are found, the streptococcus may not be responsible for the patient's illness.

Treatment and Prevention

Schmidt and Rammelkamp (1957) indicate that there are three main purposes in employing specific therapy. first, amelioration of symptoms; second, prevention of suppurative complications; and third, eradication of the organism. The sulfonamide drugs limit the activity of the group A streptococci, patients are frequently improved, and complications are undoubtedly reduced. However, they cannot be relied upon to eradicate the organisms from the nasopharyngeal areas, and a carrier state often follows their use McCarty (1954) reported detection of certain strains of group A streptococcus that were resistant to the sulfonamides. However, with the introduction of penicillin, eradication of the organism has been possible, and little evidence of resistant strains has been forthcoming. Penicillin therefore remains the drug of choice for the treatment of group A streptococcal infections. A minimum of 10 days of treatment is advocated in order to prevent suppurative complications and to eliminate the organisms

In the face of complications, cultures and sensitivity tests will indicate the need for further antibiotic therapy Various preparations of penicillin are effective, and although parenteral routes give more assurance of adequate dosage, oral administration may be employed. Oral doses recommended are 250,000 units three times a day for 10 days In the presence of penicillin sensitivity the broad-spectrum antibiotics are highly effective in treating streptococcal infections. The treatment of rheumatic fever and glomerular nephritis will not be discussed here, but preventive measures indicate that adequate

treatment of streptococcal infections with complete eradication of the organism is effective in reducing or preventing these nonsuppurative complications. Schmidt and Remmelkamp (1957) recommend continuous prophylaxis for life with sulfonamides or antibiotics in order to provide protection to known rheumatic individuals. These same recommendations are made for individuals with chronic nephritis in whom the risk of recurrent infection is considered high.

DIPHTHERIA

Epidemiology

Diphtheria is caused by *Corynebacterium diphtheriae* and is characterized by a membranous lesion on the tonsils, pharynx, and adjacent tissues. Although not commonly seen in everyday practice today, the alert physician must think about this serious disease, particularly when faced with severe toxemia and membranous exudative lesions. There is a constant danger of becoming complacent about diphtheria which fortunately now may be listed among the rare infectious diseases The disease, however, will occur in incompletely immunized individuals or where failure to give booster inoculations has allowed immunity to reach a low point The disease is said to be rare in the first six months of life, but this is based on the fact that most mothers have transmitted immunity to their offspring The incidence of positive Schick tests among adults is increasing, and we must become more aware of the possibility of diphtheria occurring early in infancy

The disease reaches its peak between the second and fifth years, following which there is a decline in the incidence However, an older age group is appearing, probably as a result of extensive active immunization of infants and preschool children The continued use of booster inoculations is very important in preventive medicine

Clinical Features

A clinical spectrum is recognized in diphtheria, the disease may be extremely mild and only discovered by bacterial cultures. The patient may complain of a catarrhal inflammation, and no evidence of membrane can be detected. This type of clinical manifestation occurs in partially immunized individuals. In the more severely involved patient, fever is as a rule low grade, ranging from 38.3° to 39.4° C. The pharyngeal and tonsillar tissues may be swollen with slight enlargement of the lymph nodes. The patient rarely complains of sore throat, and within 24 hours a small grayish-white exudate appears on the surface of the tonsils or pharynx. The exudate is similar to that commonly seen in follicular tonsillitis but tends to coalesce and spread rapidly over the tonsillar pillars, uvula, soft palate, and posterior pharyngeal wall. The exudate in diphtheria is often more extensive than that seen in non-bacterial and in streptococcal pharyngitis. A bloody serous discharge may exude from the membrane, and the odor is offensive. Cervical node enlargement may lead to marked swelling of the neck tissues with difficulty in swallowing, noisy breathing, nasal voice, or complete aphonia. Extreme toxicity should always lead the clinician to consider diphtheria.

Complicating secondary infection with streptococci must always be considered. Obstructive symptoms with laryngeal involvement constitute a serious complication in diphtheria and this syndrome is often suggested by a hoarse, brassy cough with evidences of stridor on both expiration and inspiration. The patient becomes restless and anxious, with episternal and subcostal retraction. Pneumonia may be present, particularly in association with the laryngeal forms of diphtheria. It is rarely caused by the *C. diphtheriae*, but other organisms may also be responsible.

Treatment

Diphtheria should be treated at once on the basis of clinical grounds even before positive cultures are returned, since any delay in therapy may lead to irreversible changes which may be prevented by the early administration of antitoxin. For illnesses of moderate severity 10,000–20,000 units of antitoxin are recommended; in the more severely involved patient 20,000–40,000 units should be given intramuscularly and intravenously. Neutralization of free toxin only takes place, and no effect occurs on that which is already bound by the body cells. Antibiotic therapy may be of great value in eradicating the organisms and in prevention of complications. Penicillin should be given in full therapeutic doses for at least 10 days.

PERTUSSIS

Introduction

Whooping cough or pertussis still occupies an important position with respect to morbidity and mortality in the first year of life, causing more deaths in this age group than measles, scarlet fever, diphtheria, and poliomyelitis together. Inasmuch as we are concerned with the etiologic approach to respiratory diseases, a brief discussion of whooping cough is warranted

In the early stages of this disease there is no way clinically to differentiate whooping cough from cough caused by many other etiologic agents. *Hemophilus influenzae* organisms may also be responsible for coughs and colds which are at times indistinguishable from the illness caused by *Bordetella pertussis* and *B parapertussis* The disease is serious in the first six months of life when most of the mortality occurs In this period it must be differentiated from diseases such as cystic

fibrosis of the pancreas with pulmonary complications. Although a high white count with a predominant lymphocytosis may be helpful, specific nasopharyngeal cultures are invaluable in making an accurate diagnosis in this disease.

Diagnosis and Treatment

Early diagnosis is important, particularly because early treatment may do a great deal to decrease the severity and mortality in infections caused by these organisms The severity and duration of illness may be sharply affected by antibiotic therapy, which should be presented to the patient in the early preparoxysmal stages of the disease If we are alerted to this condition and employ clinical bacteriologic methods, it is possible that a great deal can be accomplished in the management of patients with whooping cough The broad-spectrum antibiotics, such as chloramphenicol and oxytetracycline, have been used with some success in early pertussis. Specific antiserum, both human and rabbit, is available in concentrated gamma globulin preparations, in severely ill infants or in infants threatened by pertussis, daily doses of antiserum may be lifesaving A high premium is placed on early diagnosis in order that specific antiserum in infants and antibiotics in all patients may be employed at the earliest possible moment. Felton (1957) emphasizes that effective prophylaxis is the ultimate key to the eradication of whooping cough

REFERENCES

Anderson, J S, Happold, F C; McLeod, J W, and Thomson. J G (1931). On the existence of two forms of diphtheria bacillus—*B. diphtheriae gravis* and *B. diphtheriae mitis*—and a new medium for their differentiation and for the bacteriological diagnosis of diphtheria, *J. Path & Bact*, 34 667

Bradford, W. L. (1932): The tonsils in scarlet fever, in diphtheria, and in other communicable diseases In Kaiser, A. D., ed., *Children's Tonsils In or Out.* J. B. Lippincott Co., Philadelphia, p. 140.

Bradford, W. L., and Slavin, B. (1940): Nasopharyngeal cultures in pertussis, *Proc. Soc. Exper. Biol. & Med.*, 43:590.

Brahdy, M B.; Lenarsky, M.; Smith, L. W.; and Gaffney, C. A. (1935): A rapid method for the identification of diphtheria bacilli, *J.A M.A.*, 104:1881.

Breese, B. B. (1953): Treatment of beta hemolytic streptococci infections in the home: Relative value of available methods, *J.A.M.A.*, 152:10.

Breese, B. B., and Disney, F. A (1954): The accuracy of diagnosis of beta streptococcal infections on clinical grounds, *J. Pediat.*, 44.670.

Committee on Immunization and Therapeutic Procedures for Acute Infectious Diseases (1952), *Am Acad. Pediat*

Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis of the American Heart Association (1955). Prevention of rheumatic fever and bacterial endocarditis through control of streptococcal infection, *Circulation*, 11 317

Coulter, J E. (1952): Rheumatic fever and streptococcal illness in two communities in New York State, *Milbank Mem Fund Quart.*, 30 341.

Cruickshank, R (1953) Treatment of whooping cough with antibiotics, report of Whooping Cough Subcommittee of the Medical Research Council, *Lancet*, 1 1109

Darrow, D C, and Yannet, H (1935) Symptomatic therapy in malignant diphtheria, *Am J Dis Child*, 64 60

Denny, F W; Wannamaker, L W, and Hahn, E O (1953) Comparative effects of penicillin, aureomycin and terramycin on streptococcal tonsillitis and pharyngitis, *Pediatrics*, 11 7

Dingle, J H, Rammelkamp, C. H, and others (1953) A study of illnesses in a group of Cleveland families I Plan of study and certain general observations, *Am J Hyg*, 58 16

Dutkowski, S P; Stevenson, E, and Campbell, J M (1943) An epidemic of rheumatic fever in a children's institution following an outbreak of acute tonsillitis, *J A M A*, 121 991

Evans, A S. (1958): Adenovirus infections in children and young adults, with comments on vaccination, *New England J Med*, 259:464.

Felton, Harriet M (1957): Pertussis, current status of prevention and treatment, Respiratory Disorders, *Pediat Clin. North America* (Feb), p. 271.

Flotsdorf, E. W.; McGuinness, A C.; Kimball, A C , and Armstrong, J. G. (1941): Studies with pertussis VII Preparation and assay of hyperimmune human serum, *J Pediat*, 19 638

Frobisher, M., Jr (1943): Etiology of malignant diphtheria, *Am. J. Pub Health*, 33 1244.

Godfrey, E. S. (1932) Study in the epidemiology of diphtheria in relation to the active immunization of certain age groups, *Am. J Pub. Health*, 22:237.

Hollinger, N. F. (1959): Streptococcal infections Presented at Am Acad. Ped , San Francisco, Calif.

Karelitz, S , Wasserman, L R ; and Moloshok, R E (1947) Penicillin in treatment of diphtheria and diphtheria carriers, *J. Pediat.*, 30.18

Livingood, C. S , Perry, D. J , and Forrester, J S (1946) Cutaneous diphtheria Report of 140 cases, *J Invest Dermat*, 7.341.

McCarty, M (1954) *Streptococcal Infections* Columbia University Press, New York.

Major, R H (1932): *Classic Descriptions of Disease*, 2d ed Charles C Thomas, Publisher, Springfield, Ill , pp. 165, 171

Mortimer, E A , and Rammelkamp, C. H (1956) Prophylaxis of rheumatic fever, *Circulation*, 14 1144.

Naiditch, M S , and Bower, A G (1954). Diphtheria A study of 1,433 cases observed during a ten-year period at the Los Angeles County Hospital, *Am J Med*, 17 229

Park, W H (1937) Duration of immunity against diphtheria achieved by various methods, *J A M.A* , 109.1681

Powers, G F , and Boisvert, P L (1944) Age as a factor in streptococcosis, *J. Pediat*, 25.481

Rammelkamp, C H (1955) The natural history of streptococcal infections, *Bull New York Acad Med.*, 31:103

Rantz, L. A. (1959): Streptococcal diseases. Presented at Am Acad. Ped., San Francisco, Calif.

Rantz, L. A.; Maroney, M.; and DiCaprio, J. M. (1953): Hemolytic streptococcal infection in childhood, *Pediatrics*, 12:498

Schick, B. (1913): Die Diphtherietoxin-Hautreaktion des Menshchen als Vorprobe der prophylaktischen diphtheriheilserum-injektion, *München. med. Wchnschr.*, 60.2608.

Schmidt, W. C., and Rammelkamp, C. H. (1957): Bacterial infections of the nasopharynx, with particular reference to the prevention of rheumatic fever and glomerulonephritis. Respiratory Disorders, *Ped. Clin North America* (Feb.), p. 139

Schwenkter, F. F., and Noel, W. W. (1930): The treatment of the circulatory failure of diphtheria, *Bull. Johns Hopkins Hosp*, 46:359.

Smith, T (1909) Active immunity produced by so-called balanced or neutral mixtures of diphtheria toxin and antitoxin, *J. Exper Med.*, 11:241

U.S National Office of Vital Statistics (1956): Death rates by age, race, and sex, United States, 1900–53 Whooping Cough, Vital Statistics—Special Reports, 43, (7), U S Government Printing Office, Washington, D C.

Updyke, E L, and Frobisher, M, Jr. (1947). A study of bacterial synergism with reference to the etiology of malignant diphtheria, *J Bact*, 54 619

Wannamaker, L W; Rammelkamp, C H, and others (1951) Prophylaxis of acute rheumatic fever by treatment of the preceding streptococcal infection with various amounts of depot penicillin, *Am. J. Med*, 10 673

Chapter Twelve

FUNGAL INFECTIONS OF THE RESPIRATORY SYSTEM AND PRIMARY TUBERCULOSIS

INTRODUCTION

A brief discussion of two diseases caused by fungal agents is pertinent to the main theme that is being elaborated in this book. Largely by means of skin tests and also as a result of clinical and epidemiologic surveys, both of these fungal diseases are now recognized as producing inapparent illness in a large percentage of those infected. Both of these agents cause a mild influenza-like illness, followed by rapid recovery. The two fungal diseases are coccidioidomycosis and histoplasmosis. The highly endemic centers for these diseases are more than 2000 miles apart and have quite divergent or opposite types of climatology. Coccidioidomycosis is markedly epidemic in the San Joaquin Valley in California which is extremely dry, whereas histoplasmosis is concentrated in the mid-central states, focusing around the junction of the Ohio and Mississippi rivers, with 80 to 90 per cent of the population reacting positively in certain areas of Tennessee, Kentucky, and Missouri. These states are recognized as rainy,

very fertile, agricultural areas. In spite of highly concentrated endemic areas, shifts in population and travel habits have resulted in a wide dispersion of these diseases which are now recognized in almost all states in the Union. Emphasis is being placed on these two diseases, which are known to be caused by *fungal agents*, because *they may be primary invaders* of the respiratory passages and produce mild illness in man. They may readily be confused with mild, moderate, or severe respiratory disease.

Physicians in the heart of the San Joaquin Valley state that new families coming to the area will acquire coccidioidomycosis; a "flu-like" illness, lasting but a few days, is the *principal clinical manifestation. Because of a distinct and well-*established etiology in both of these diseases, they will be discussed as separate entities.

COCCIDIOIDOMYCOSIS

This disease is caused by a specific fungus known as *Coccidioides immitis* whose natural environment is the soil where it appears as a fluffy mycelium growth of septate hyphae. These hyphae are highly contagious and are air-borne in the dry summer months, particularly in areas of new housing developments or where contaminated soil is under cultivation. For the most part, *C. immitis produces disease primarily* in the respiratory passages. The primary illness follows exposure to contaminated dust in one, two, or three weeks. The patient becomes ill with malaise, low-grade fever, and cough. However, infection may be so mild that 60–70 per cent of the patients escape clinical manifestations and only by the appearance of skin sensitivity is it possible to determine that *infection has taken place* In many ways the sequence of events is similar to that which is known to occur in primary tuberculosis. It is variously estimated that 30–40 per cent of exposed patients who become infected develop an afebrile ill

ness that has been called San Joaquin Valley fever, valley fever, or desert fever.

Clinical Features

Although fever and cough are the primary symptoms, thoracic pain may develop in many patients who have more severe manifestations The cough may be moderately productive, and hemoptysis occasionally occurs in the acute stage of the disease, but does not have the implications so commonly associated with this symptom in tuberculosis. In the acute stages of valley fever physical examination is quite unrevealing, although some findings may be present in approximately 25 per cent of the patients. When studied roentgenologically, pulmonary consolidations and slight effusions are found in a minority of the patients. Progressive and disseminated granulomatous disease occurs in only a small percentage of patients. Failure to localize with lymphatic and hematogenous spread produces this catastrophic form of illness in about 0 25 per cent of white-skinned patients whereas *the incidence in dark-skinned patients may be 10–30 times* as high.

Originally, both coccidioidomycosis and histoplasmosis were considered to be highly fatal diseases as the earliest descriptions came from the autopsy table. However, in 1938 Dickson and Gifford described the primary form of the disease and pointed out the benign nature of this infection Nearly every organ in the body may be involved in the disseminated form of the disease A *fulminating* course is evident with sepsis and meningitis in the most severe cases Osteomyelitis, skin involvement, and other extrapulmonary organs are frequently involved in the chronic granulomatous type of infection. The coccidioidin skin test may be negative during the acute disseminated form of this disease. However, serologic tests as a rule are positive and have a great deal of prognostic

very fertile, agricultural areas. In spite of highly concentrated endemic areas, shifts in population and travel habits have resulted in a wide dispersion of these diseases which are now recognized in almost all states in the Union. Emphasis is being placed on these two diseases, which are known to be caused by fungal agents, because they may be primary invaders of the respiratory passages and produce mild illness in man. They may readily be confused with mild, moderate, or severe respiratory disease.

Physicians in the heart of the San Joaquin Valley state that new families coming to the area will acquire coccidioidomycosis; a "flu-like" illness, lasting but a few days, is the principal clinical manifestation. Because of a distinct and well-established etiology in both of these diseases, they will be discussed as separate entities.

COCCIDIOIDOMYCOSIS

This disease is caused by a specific fungus known as *Coccidioides immitis* whose natural environment is the soil where it appears as a fluffy mycelium growth of septate hyphae. These hyphae are highly contagious and are air-borne in the dry summer months, particularly in areas of new housing developments or where contaminated soil is under cultivation. For the most part, *C. immitis* produces disease primarily in the respiratory passages. The primary illness follows exposure to contaminated dust in one, two, or three weeks. The patient becomes ill with malaise, low-grade fever, and cough. However, infection may be so mild that 60–70 per cent of the patients escape clinical manifestations and only by the appearance of skin sensitivity is it possible to determine that infection has taken place. In many ways the sequence of events is similar to that which is known to occur in primary tuberculosis. It is variously estimated that 30–40 per cent of exposed patients who become infected develop an afebrile ill-

ness that has been called San Joaquin Valley fever, valley fever, or desert fever.

Clinical Features

Although fever and cough are the primary symptoms, thoracic pain may develop in many patients who have more severe manifestations. The cough may be moderately productive, and hemoptysis occasionally occurs in the acute stage of the disease, but does not have the implications so commonly associated with this symptom in tuberculosis In the acute stages of valley fever physical examination is quite unrevealing, although some findings may be present in approximately 25 per cent of the patients. When studied roentgenologically, pulmonary consolidations and slight effusions are found in a minority of the patients Progressive and disseminated granulomatous disease occurs in only a small percentage of patients. Failure to localize with lymphatic and hematogenous spread produces this catastrophic form of illness in about 0 25 per cent of white-skinned patients whereas the incidence in dark-skinned patients may be 10–30 times as high.

Originally, both coccidioidomycosis and histoplasmosis were considered to be highly fatal diseases as the earliest descriptions came from the autopsy table However, in 1938 Dickson and Gifford described the primary form of the disease and pointed out the benign nature of this infection Nearly every organ in the body may be involved in the disseminated form of the disease. A fulminating course is evident with sepsis and meningitis in the most severe cases Osteomyelitis, skin involvement, and other extrapulmonary organs are frequently involved in the chronic granulomatous type of infection. The coccidioidin skin test may be negative during the acute disseminated form of this disease. However, serologic tests as a rule are positive and have a great deal of prognostic

significance. The extensive form of the disease is usually associated with high complement-fixation titers. Rising titers are viewed with alarm whereas the declining titers augur well for a favorable outcome. Smith and co-workers (1946) studied 1351 primary infections and recorded a wide clinical spectrum of involvement with approximately 40 per cent of the patients presenting symptoms, whereas 60 per cent were symptom-free. The latter group were detected by means of skin hypersensitivity to coccidioidin and also by means of roentgenographic studies, revealing pulmonary infiltrations of a nontuberculous nature. No attempt will be made to present details regarding the many different clinical pathologic features of this disease.

Treatment

The treatment of coccidioidomycosis is unsatisfactory to date so far as specific therapy is concerned. Favorable reports regarding the use of amphotericin B have been made by Littman and associates (1958), who used this drug intravenously in patients with acute and chronic coccidioidal infection. In the nondisseminating forms of coccidioidomycosis recovery is the rule and no therapy is necessary. However, therapy of a specific nature would be highly desirable in the disseminated form of this disease. Until recently, prolonged bed rest was the only treatment for these patients. Exceptions occurred when surgical extirpation of pulmonary infection could be accomplished. Littman and associates (1958) cite several unsuccessful therapeutic agents which have received clinical trial, the list is long and includes nearly all of the antibiotics.

Amphotericin B, an antifungal antibiotic, was isolated in 1955 by Gold and associates (1956). This antibiotic, first isolated in Venezuela, is elaborated by a species of streptomyces. The intravenous use of this medication produces

some toxic effects, particularly on the kidneys, but no such effects are observed on the heart, liver, or neurologic system Blood levels showed that the drug was absorbed poorly from the gastrointestinal tract. This drug was employed with benefit in patients who were severely ill with systemic forms of coccidioidomycosis. Fortunately the great majority of patients infected by this fungus recover without event and apparently remain immune for the balance of their lives.

HISTOPLASMOSIS

This primary respiratory tract infection, caused by *Histoplasma capsulatum*, is a widespread disease in the United States with estimates of involvement as high as one-fifth of the population. The extensive nature of this disease was not recognized until about 20 years ago when the occurrence of nontuberculous pulmonary calcifications in certain areas of the country was recognized. The importance of fungi as pathogenic agents for man has only recently been emphasized, and such emphasis has resulted in part from the remarkable changes in therapy that have occurred with the advent of antibiotics Histoplasmosis has now assumed a most prominent role, occurring with high frequency in certain densely populated areas of this country. The most concentrated areas, as shown by skin sensitivity to histoplasmin, are the central Mississippi and Ohio River valleys However, sporadic cases have been discovered in nearly every state of the Union, as well as Canada and many foreign countries Travel and migrations have undoubtedly accounted for the distribution of patients throughout the United States.

Furcolow (1958) points out that because histoplasmosis mimics other diseases we have been slow to recognize its importance in the over-all spectrum of illness. Even in its milder forms, he draws attention to the fact that its differentiation from common maladies, such as influenza and unexplained

fever, was impossible until diagnostic aids such as the histoplasmin test became available. The long and widespread use of the tuberculin test led many physicians to assume that pulmonary calcifications were caused by tuberculosis. However, with the increased use of various skin tests, it became apparent that many pulmonary calcifications were unrelated to tuberculosis. By 1945, workers at Vanderbilt University clearly demonstrated the wide clinical spectrum of histoplasmosis, pointing out that many pulmonary calcifications were nontuberculous and that many patients with histoplasmosis were indeed quite well. As in other diseases, first impressions were gained from the overwhelming disseminating forms of the disease that were studied at the autopsy table. It was natural to assume that this disease was uniformly fatal. However, the histoplasmin test quickly demonstrated that this disease, like coccidioidomycosis and tuberculosis, appears in inapparent form in the majority of patients infected.

Clinical Features

It is known that many infections are acquired without causing overt disease and that the milder forms are characterized by an influenza-like illness lasting but a few days, with malaise, fever, and slight cough or chest pain being the classic early findings. These are similar to the first and earliest clinical manifestations of coccidioidomycosis. Although the physical examination in these patients is frequently unrevealing, an x-ray examination will show nodular infiltrations which usually calcify. These lesions may be widespread in patients who recover, as shown in Figure 18.

In the moderately severe forms of this disease the illness, described as influenza-like, may persist from 5 to 15 days and simulate atypical pneumonia with cough and chest pain the prominent symptoms. Illnesses of this type have been common in the summer months, and often a history of having

fever, was impossible until diagnostic aids such as the histoplasmin test became available. The long and widespread use of the tuberculin test led many physicians to assume that pulmonary calcifications were caused by tuberculosis. However, with the increased use of various skin tests, it became apparent that many pulmonary calcifications were unrelated to tuberculosis. By 1945, workers at Vanderbilt University clearly demonstrated the wide clinical spectrum of histoplasmosis, pointing out that many pulmonary calcifications were nontuberculous and that many patients with histoplasmosis were indeed quite well. As in other diseases, first impressions were gained from the overwhelming disseminating forms of the disease that were studied at the autopsy table. It was natural to assume that this disease was uniformly fatal. However, the histoplasmin test quickly demonstrated that this disease, like coccidioidomycosis and tuberculosis, appears in inapparent form in the majority of patients infected.

Clinical Features

It is known that many infections are acquired without causing overt disease and that the milder forms are characterized by an influenza-like illness lasting but a few days, with malaise, fever, and slight cough or chest pain being the classic early findings. These are similar to the first and earliest clinical manifestations of coccidioidomycosis. Although the physical examination in these patients is frequently unrevealing, an x-ray examination will show nodular infiltrations which usually calcify. These lesions may be widespread in patients who recover, as shown in Figure 18.

In the moderately severe forms of this disease the illness, described as influenza-like, may persist from 5 to 15 days and simulate atypical pneumonia with cough and chest pain the prominent symptoms. Illnesses of this type have been common in the summer months, and often a history of having

visited farms or chicken coops is obtained Epidemics of histoplasmosis have been recorded, and Furcolow (1958) states that more than 30 epidemics of histoplasmosis involv-

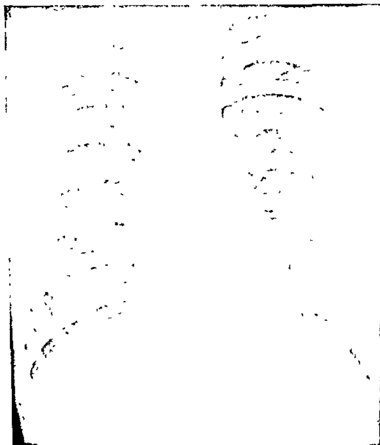


Figure 18. A roentgenogram of the lungs of a child illustrating the multiple areas of calcification that occur in histoplasmosis (This illustration was obtained through the courtesy of Dr Amos Christie, Vanderbilt University, Nashville, Tenn, and is published by permission from Irvine McQuarrie, *Brennemann's Practice of Pediatrics,* W F Prior Co, Inc, Hagerstown Md, 1957)

ing over 400 persons are now described. These have occurred primarily in the United States, but a few have been reported in South America. In epidemics the illness is characterized by a wide clinical spectrum varying from inapparent and very mild to extremely severe disease.

It has been emphasized that the most severely ill patients are those who have a history of heavy exposure. The characteristic *roentgenographic picture is one of nodular infiltration* diffusely scattered throughout both lungs with hilar lymph node enlargement. In the disseminated form, enlargement of the liver and spleen, high fever, and prostration are the outstanding symptoms This latter type of illness occurs in the very young, in contrast to the acute epidemic forms which tend to occur in adults The onset is usually rapid but may be insidious. The course, however, tends to be progressive with fever and increasing signs of toxicity, and with x-ray *findings characterized by fine infiltrations* resembling those seen in miliary tuberculosis

Chronic forms of the disease are not common, and the symptomatology is similar to chronic tuberculosis, with identical x-ray findings. The chronic form of the disease has its ups and downs with intermittent, influenza-like illnesses A fatal termination after many years of recurring illness is the usual outcome for these patients.

The organism of histoplasmosis is found in the soil and may be transmitted directly to man and animals Infection is thought to take place by direct inhalation from specific areas rather than being widely air-borne The fungus appears to grow most luxuriantly in moist shady areas and particularly in enclosed areas such as chicken coops, pigeon roosts, storm cellars, silos, and places *in which humidity and temperature* conditions favor growth of fungi As is the case with coccidioidomycosis, the degree of illness appears to be related

directly to the number of organisms which the patient inhales.

Diagnostic features require a consideration of histoplasmosis in most influenza-like illnesses, particularly when pulmonary lesions are present. Prolonged pulmonary illnesses extending beyond the influenza period of a few days should strongly suggest this disease. Epidemics occur primarily in the summer months, and the focal point may often be revealed by the history. The disseminated forms of the disease are so acute and overwhelming that they may well be confused with such illnesses as leukemia or typhoid fever. Complement-fixation and precipitin tests are invaluable in the diagnosis of histoplasmosis, but four to six weeks may elapse before titers rise or the skin test becomes positive. Serologic tests may be positive only during the acute phase, and a rising titer, as in coccidioidomycosis, suggests a poor prognosis. The skin test is a most valuable aid in the diagnosis of this disease, and its use must be interpreted with the same considerations that are given to the tuberculin test.

Coccidioidomycosis and histoplasmosis both cause granulomatous lesions with giant cell formation Atypical tubercle formation occurs, and confluent tubercles may produce consolidation, which is occasionally seen in all three diseases. Calcification that closely resembles the changes seen in tuberculosis occurs. Histoplasmosis has been highly refractive to treatment by drugs or antibiotics By means of tissue culture methods a comparison of antifungal properties may be made, in vitro studies indicate that amphotericin B and candicidin hold some therapeutic promise Reference was made earlier to Littman's (1958) favorable results from the intravenous use of amphotericin B in the treatment of coccidioidomycosis No treatment is required for the milder acute forms of this disease, and the prognosis is very favorable in a great majority

of the patients, the exceptions being the rare acute disseminated and some chronic forms of disease.

PRIMARY TUBERCULOSIS

Many so-called childhood forms or primary infections caused by *Mycobacterium tuberculosis* undoubtedly simulate undifferentiated respiratory disease and pass for a mild, moderate, or severe "cold" lasting varying periods of time. If it were not for the tuberculin test, we might still be unaware of the association of as serious a disease as tuberculosis with inapparent and mild forms now recognized as part of the clinical spectrum of tuberculosis, particularly in infants and children. Recent papers have emphasized that the majority of infections in children may go unrecognized clinically; only by repeated tuberculin testing, history of exposure, and additional laboratory tests including roentgenographic studies have we realized the full significance of the milder forms of this primary illness. For these reasons, a brief discussion of tuberculosis is introduced at this time because of the many similarities between this disease and primary coccidioidomycosis, histoplasmosis, and undifferentiated respiratory disease

Etiology

The tubercle bacillus is a slender, nonmotile rod, designated as *Mycobacterium tuberculosis*. There are several varieties that are identified by cultural and pathogenic characteristics. The human and bovine varieties are pathogenic for man and are probably responsible for most of the tuberculosis which we now recognize The bovine forms of the disease have been remarkably well controlled in the United States by public health measures such as periodic tuberculin testing of cattle and their subsequent elimination Pasteurization of milk has undoubtedly played an important role in this public health achievement

The Tuberculin Reaction

A positive skin reaction to tuberculin indicates that the individual has been sensitized to the protein of the tubercle bacillus. The test constitutes the most effective means available at the present time for the separation of those persons who have had a tuberculous infection from those who have not. Although it has been used for many years to detect tuberculosis, it has not been fully exploited for this purpose. We have recently become aware of the importance of repeating tuberculin tests as a means of detecting early tuberculosis; consequently, the natural history of this disease is becoming better understood Converters previously known to be negative have not only been found early in their disease but, by repeated tests, have been found to revert in a surprisingly high incidence. Interpretation of this finding is not fully understood, but it may indicate minimal infection in many individuals followed by what may be complete healing Multiple tests with purified protein derivative do not appear to produce a positive reaction per se, and may safely be employed for the earliest detection of allergy to the protein of the tubercle bacillus.

Reversal of tuberculin reaction may occur in a high percentage of individuals who develop a weakly positive reaction This fact was recorded by Dahlstrom (1940) from the Phipps Institute in a study in which he reported on the instability of the tuberculin reaction. Little evidence of clinical disease can be found by careful searching in individuals with weakly positive reactions, and roentgenographic study of the chest of these same individuals shows a high percentage with normal findings Reversal rates were highest in those with no x-ray findings. The reversion of the tuberculin reaction was found to occur in a matter of months in individuals with 2+ and 3+ reactions but in decreasing frequency as the reaction in-

creased in intensity. There would appear to be a possible relationship between the degree of reactivity and the extent of the tuberculous infection. In animals which have been infected with tubercle bacilli and followed promptly by treatment, the extent of disease can be sharply limited and likewise the skin reactivity is held to a minimal degree correlating with the extent of the pathologic lesions. Infected animals that are untreated develop severe tuberculin reactions If further study establishes a direct relationship between the degree of skin reactivity and the extent of the patient's disease, the tuberculin test will become an extremely valuable clinical tool and may even be useful in following the course of the patient's disease.

Clinical Features

No attempt will be made in this brief discussion to review the many clinical problems in tuberculosis. The main purpose of this discussion is to call attention to the fact that primary tuberculosis is probably one of the first diseases in which the wide clinical spectrum of disease was first recognized Undoubtedly many individuals acquire their first infection without any knowledge of illness, or vague and ill-defined influenza-like symptoms occur that simulate the "common cold" Cough and low-grade fever may be the only symptomatology recognized When a roentgenogram of the chest is taken, the clinician is often surprised at the extent of the patient's disease, particularly when compared to the symptoms and signs

In the first infection, inhalation of the human type of tubercle bacillus has been considered the primary route of infection. However, primary infections may arise in the intestines in an appreciable number of cases, and particularly when unpasteurized milk contaminated with bovine or human tubercle bacilli is consumed The childhood or first infec-

tion type of tuberculosis has been compared to the first subcutaneous infections of the guinea pig which are followed by lymph node involvement and progressive disease. If the pig is infected subsequently, however, at a different site such as the opposite leg, the infection will remain entirely or almost entirely localized and rarely invade the proximal lymph nodes. The first infection type of tuberculosis has been described as the acute type of disease, healing or progressing in a relatively short time as opposed to the adult or reinfection type which is much more stable and chronic. In the first infection an exudative lesion occurs with healing taking place by resolution or calcification. The reinfection type may caseate and lead to cavitation or may heal with scar formation

Treatment

In the treatment of the primary infection there are several important considerations, not the least of which is a thorough search for the source of infection. Steps directed toward elimination of further contact are extremely important in infants and small children. Rest and adequate nutrition should be supplied in the most pleasant surroundings available. Minimal asymptomatic infections in children do not warrant specific therapy, particularly if the source of infection has been promptly eliminated However, if infection is known to be early and the tuberculin reaction is moderate to marked, specific therapy should be seriously considered even in asymptomatic patients The use of isoniazid (INH) orally is highly recommended for the treatment of this type of early infection If, however, there are signs of active infection, as can be demonstrated by physical examination and roentgenographic findings, vigorous therapy is indicated, including the use of streptomycin, sodium P-aminosalicylate (PAS), and INH The dosage program should be worked out after careful evaluation of the clinical problem INH is administered orally

creased in intensity. There would appear to be a possible relationship between the degree of reactivity and the extent of the tuberculous infection. In animals which have been infected with tubercle bacilli and followed promptly by treatment, the extent of disease can be sharply limited and likewise the skin reactivity is held to a minimal degree correlating with the extent of the pathologic lesions. Infected animals that are untreated develop severe tuberculin reactions. If further study establishes a direct relationship between the degree of skin reactivity and the extent of the patient's disease, the tuberculin test will become an extremely valuable clinical tool and may even be useful in following the course of the patient's disease.

Clinical Features

No attempt will be made in this brief discussion to review the many clinical problems in tuberculosis. The main purpose of this discussion is to call attention to the fact that primary tuberculosis is probably one of the first diseases in which the wide clinical spectrum of disease was first recognized. Undoubtedly many individuals acquire their first infection without any knowledge of illness, or vague and ill-defined influenza-like symptoms occur that simulate the "common cold." Cough and low-grade fever may be the only symptomatology recognized. When a roentgenogram of the chest is taken, the clinician is often surprised at the extent of the patient's disease, particularly when compared to the symptoms and signs.

In the first infection, inhalation of the human type of tubercle bacillus has been considered the primary route of infection. However, primary infections may arise in the intestines in an appreciable number of cases, and particularly when unpasteurized milk contaminated with bovine or human tubercle bacilli is consumed. The childhood or first infec-

tion type of tuberculosis has been compared to the first subcutaneous infections of the guinea pig which are followed by lymph node involvement and progressive disease. If the pig is infected subsequently, however, at a different site such as the opposite leg, the infection will remain entirely or almost entirely localized and rarely invade the proximal lymph nodes. The first infection type of tuberculosis has been described as the acute type of disease, healing or progressing in a relatively short time as opposed to the adult or reinfection type which is much more stable and chronic. In the first infection an exudative lesion occurs with healing taking place by resolution or calcification. The reinfection type may caseate and lead to cavitation or may heal with scar formation.

Treatment

In the treatment of the primary infection there are several important considerations, not the least of which is a thorough search for the source of infection. Steps directed toward elimination of further contact are extremely important in infants and small children. Rest and adequate nutrition should be supplied in the most pleasant surroundings available. Minimal asymptomatic infections in children do not warrant specific therapy, particularly if the source of infection has been promptly eliminated. However, if infection is known to be early and the tuberculin reaction is moderate to marked, specific therapy should be seriously considered even in asymptomatic patients. The use of isoniazid (INH) orally is highly recommended for the treatment of this type of early infection If, however, there are signs of active infection, as can be demonstrated by physical examination and roentgenographic findings, vigorous therapy is indicated, including the use of streptomycin, sodium P-aminosalicylate (PAS), and INH The dosage program should be worked out after careful evaluation of the clinical problem INH is administered orally

with the total daily dose of 10 to 20 mg per kilogram of body weight. This should be given in divided doses two or three times per day. The daily oral dose of PAS is 500 mg per kilogram divided into three or four doses. The total dose of streptomycin of 10 to 20 mg per kilogram of body weight may be employed intramuscularly daily for several weeks followed by biweekly injections. Smith and Matsaniotis (1958) have used adrenal corticosteroids simultaneously with adequate antituberculous drug therapy in children with pleural effusions and report clinical and roentgenographic improvement. Their treatment program is as follows: INH (20 mg/kg/24 hr) and PAS (0.5 gm/kg/24 hr) for at least a year, prednisone (1.0 mg/kg/24 hr) for four to six weeks with diminishing doses during the ensuing two weeks

REFERENCES

Aronson, J D (1951). The fluctuation of the tuberculin reaction in different geographic areas and its relationship to resistance, *Am. Rev Tuberc*, **63**.121

Baum, G L., and Schwarz, J (1955) Coccidioidomycosis A review, *Am J M. Sc*, **230**:82

Blatman, S; Rapmund, G, Newstrand, D; and Alexander, H Microbiological study of gastric contents as an index to the state of pulmonary tuberculous lesions Personal communication.

Bunnell, I L., and Furcolow, M. L (1948) A report on ten proved cases of histoplasmosis, *Pub Health Rep*, **63** 299

Christie, A (1946) Histoplasmin sensitivity, *J Pediat*, **29** 417

Christie, A, Middleton, J G; Peterson, J C, and McVickar D L (1951) Treatment of disseminated histoplasmosis with ethyl vanillate, *Pediatrics*, **7** 7

Christie, A, and Peterson, J C (1945) Pulmonary calcification in negative reactors to tuberculin, *Am J Pub Health*, **35** 1131

Curry, F. J, and Wier, J A. (1958): Histoplasmosis: A review of one hundred consecutively hospitalized patients, *Am Rev. Tuberc. & Pul Dis.*, **77**.749.

Dahlstrom, A. W. (1940): The instability of the tuberculin reaction, *Am. Rev. Tuberc.*, **42**:471.

Dickson, E C., and Gifford, M A. (1938): *Coccidioides* infection (coccidioidomycosis). II The primary type of infection, *Arch Int. Med*, **62**.853

Dubos, R. J. (1956). Symposium on tuberculosis in infancy and childhood, *Am. Rev. Tuberc.*, **74**, no 2 (part 2) 5

Forbus, W. D., and Besterbreurtje, A. M (1946) Coccidioidomycosis: A study of 95 cases of the disseminated type with special reference to the pathogenesis of the disease, *Mil Surgeon*, 99 653

Friedman, L; Smith, C E, Roessler, W G; and Berman, R J (1956): The virulence and infectivity of twenty-seven strains of *Coccidioides immitis*, *Am J Hyg*, **64** 198

Furcolow, M L (1956). The clinical diagnosis of histoplasmosis, *Postgrad Med*, **20**.349.

Furcolow, M L. (1958) Histoplasmosis Seminar Report, Summer 1958, p 23 (Published by Merck Sharp and Dohme)

Furcolow, M L, and Brasher, C. A (1956). Chronic progressive (cavitary) histoplasmosis as a problem in tuberculosis sanatoriums, *Am. Rev. Tuberc.*, **73** 609

Furcolow, M L; Mantz, H, and Lewis, I (1947) The roentgenographic appearance of persistent pulmonary infiltrations associated with sensitivity to histoplasmin, *Pub. Health Rep*, **62** 1711

Galten, J, and Hamman, L (1913). The subsequent history of 1000 patients who received tuberculin tests, *Bull, Johns Hopkins Hosp*, **24** 180

Gifford, M A (1942) Coccidioidomycosis in Kern County, California, *Proc Sixth Pacific Sc. Congr*, *1939*, **5** 791

Gold, W, Stout, H A, Pagano, J. F, and Donovick, R (1956) Amphotericins A and B, antifungal antibiotics produced by a streptomycete I In vitro studies In *Antibiotics Annual 1955–1956*, Medical Encyclopedia, New York, p 579

Grocott, R. G. (1955): A stain for fungi in tissue sections and smears using Gomori's methenamine—silver nitrate technic. *Am. J. Clin. Path.*, 25:975.

Hild, J. R. (1942): Histoplasmosis in infancy, *Am. J. Dis. Child.*, 63:131.

Huntington, R. W., Jr. (1957): Diagnostic and biologic implications of the histopathology of coccidioidomycosis, Pub. Health Service Publ. #175, Proc. Symposium on Coccidioidomycosis

Johnson, H., and Batson, O. R (1948): Benign pulmonary histoplasmosis: Case report with brief review of literature, *Dis. Chest*, 14:517.

Kritzer, M. D.; Biddle, M.; and Kessel, J. F. (1950): An outbreak of primary pulmonary coccidioidomycosis in Los Angeles County, California, *Ann Int. Med.*, 33:960

Kundstadter, L. H; Whitcomb, F. C.; and Milzer, A (1949): Primary histoplasmosis with recovery of *H. capsulatum* from the blood and bronchial secretions, *J. Lab. & Clin Med.*, 34 1290.

Lehan, *P. H*, and Furcolow, M. L. *(1957). Epidemic histoplasmosis, J. Chronic Dis., 5*·489

Lehan, P H.; Yates, J L, Brasher, C. A; Larch, H W., and Furcolow, M L (1957) Experiences with the therapy of sixty cases of deep mycotic infections, *Dis. Chest.* 32.597

Littman, M L, Horowitz, P. L, and Swadey, J G (1958) Coccidioidomycosis and its treatment with amphotericin B, *Am. J Med*, 24 568

Littman, M L, and Zimmerman, L E (1956) *Cryptococcosis, Torulosis or European Blastomycosis* Grune & Stratton, New York, pp 1–205

Loosli, C G (1955) Histoplasmosis Some clinical, epidemiological and laboratory aspects, *M Clin North America*, 39 171

Mead, C I *(1951). Coccidioidomycosis in children J A M A*, 146 85

O'Leary, D J, and Curry, F J (1956) Coccidioidomycosis A

review and presentation of 100 consecutively hospitalized patients, *Am. Rev. Tuberc.*, **73** 501.

Palmer, C. E. (1945): Nontuberculous pulmonary calcification and sensitivity to histoplasmin, *Pub. Health Rep.*, **60**·513

Paretzky, M. (1936): The disappearance of specific skin hypersensitiveness in tuberculosis, a report based on 80 cases, *Am Rev. Tuberc.*, **33**.370.

Parsons, R. J , and Zarafonetis, C. J D (1945): Histoplasmosis in man. Report of seven cases and review of seventy-one cases, *Arch. Int. Med*, **75**:1.

Peizer, L R ; Chaves, A D.; and Widelock, D (1957) The effects of early isoniazid treatment in experimental guinea pig tuberculosis, *Am Rev Tuberc. & Pul. Dis*, **76** 732

Polk, J D ; Brasher, C A ; de Castro, J , and Buckingham, W. W (1956): The surgical treatment of pulmonary histoplasmosis with an evaluation of MRD-112 as a possible adjunct, *J. Thoracic Surg.*, **31**:148

Puckett, T F. (1953). Pulmonary histoplasmosis: A study of twenty-two cases with identification of *H. capsulatum* in resected lesions, *Am Rev. Tuberc*, **67**·453

Robinson, A , Meyer, M.; and Middlebrook, G (1955): Tuberculin hypersensitivity in infants treated with isoniazid, *New England J Med.*, **252**:983

Schwarz, J , and Muth, J. (1951): Coccidioidomycosis A review, *Am J. M. Sc*, **221**·89.

Silverman, F N. (1950): Pulmonary calcification Tuberculosis, histoplasmosis, *Am J Roentgenol*, **64** 747.

Smith, C. E , Whiting, E G.; Baker, E E ; Rosenberger, H G ; Beard, R. R ; and Saito, M. T (1948) The use of coccidioidin, *Am. Rev Tuberc*, **57** 330

Smith, C E (1940) Epidemiology of acute coccidioidomycosis with erythema nodosum ("San Joaquin" or "valley fever"), *Am J Pub Health*, **30** 600.

Smith, C E (1942) An epidemiological study of acute coccidioidomycosis with erythema nodosum, *Proc Sixth Pacific Sc Congr*, *1939*, **5** 797

Smith, C. E. (1942): Parallelism of coccidioidal and tuberculous infections, *Radiology*, 38:643.

Smith, C. E.; Beard, R R ; Rosenberger, H. G ; and Whiting, E. G. (1946): Effect of season and dust control on coccidioidomycosis, *J.A.M.A.*, 132:833.

Smith, C. E ; Beard, R. R ; Whiting, E. G.; and Rosenberger, H. G. (1946): Varieties of coccidioidal infection in relation to the epidemiology and control of the diseases, *Am J. Pub Health*, 36:1394.

Smith, C. E.; Saito, M. T., Beard, R R.; Kepp, R. McF.; Clark, R W.; and Eddie, B. U. (1950): Serological tests in the diagnosis and prognosis of coccidioidomycosis, *Am. J. Hyg.*, 52:1.

Smith, C. E ; Saito, M T ; and Simons, S. A. (1956): Pattern of 39,500 serologic tests in coccidioidomycosis, *J.A M A.*, 160: 546

Smith, M. H D , and Matsaniotis, N. (1958): Treatment of tuberculous pleural effusions with particular reference to adrenal corticosteroids, *Pediatrics*, 22 1074

Straub, M , and Schwarz, J (1955): The healed primary complex in histoplasmosis, A. J Clin Path., 25 727

Tuberculosis Vaccines Clinical Trials Committee (1956). B C G and vole vacillus vaccines in the prevention of tuberculosis in adolescents, *Brit. M J* (Feb 25), p 413

Tukey, J W , DuFour, E H ; and Seibert, F (1950) Lack of sensitization following repeated skin tests with standard tuberculin (PPD-S), *Am Rev. Tuberc* , 62A 77

Willett, F M , and Weiss, A (1945) Coccidioidomycosis in southern California, report of a new endemic area with a review of 100 cases, *Ann Int Med* , 23 349

Chapter Thirteen

THE COMMON COLD AND ALLERGIC RHINITIS

INTRODUCTION

In spite of the fact that the common cold represents the commonest illness of man, its definition becomes almost a personal matter, since it is an illness with which we are all intimately acquainted. The common cold per se is not a serious disease, but because of its ubiquitous and banal nature it remains a problem that has been influenced very little by the advances in scientific medicine Colds contribute in no small measure to the miseries of man and undoubtedly play their most important role as precursors of serious disease. We recognize that nearly all of man's infectious diseases may become clinically manifest by symptoms that are often attributed to "colds." Specific infections, such as scarlet fever, diphtheria, and whooping cough, may all begin as a "kind of cold." Q fever, influenza, or psittacosis and such diseases as primary tuberculosis may simulate closely the symptom complex of the common cold

We know too little of the importance of this common disease and its role in the pathogenesis of many serious and even *killing infections Although conclusive proof is still lacking,*

evidence is at hand which would tend to incriminate the common cold *or one of its cousins* as being directly responsible for the tragic and unexpected crib deaths in infancy. (See Chapter Nine.) Statements which one frequently sees in the newspapers tend to minimize the importance of the common cold with emphasis on the consequences. Such a clipping reads as follows: "Then came the tragic years that Eleanor Roosevelt recalls her 'trial by fire.' Her husband's illness—first diagnosed as a cold—turned out to be infantile paralysis." Another news item dated January 23, 1953, reads as follows: "The disease, not yet positively identified but which starts much like a common cold and then kills its infant victims within a few hours, claimed its sixth victim [in one week] in Tacoma, Washington, yesterday."

CLINICAL FEATURES

Definition of the common cold is complicated by the fact that certain chemical irritants, allergens, and vasomotor responses of the nasopharyngeal membranes are difficult indeed to separate or differentiate from true infectious colds. In spite of the difficulties and complexities the common cold may be simply defined as an acute nasopharyngitis of unknown etiology. The primary symptoms include irritation and dryness of the nasal passages, often associated with chilly sensations and muscular aching. The feeling of congestion with sneezing is frequently accompanied by a watery discharge from the nose. Hoarseness and nasal voice are soon evident, and the patient complains of irritability, itching of the eyes, loss of appetite, and occasionally headache. These symptoms may persist from a few hours to a week, and many so-called colds seem to be aborted with or without treatment in a matter of hours. The patient frequently forgets the prodromal symptoms of a cold because they often disappear as quickly as they came, particularly following a night of rest.

The newborn baby appears to be relatively immune to colds for the first few weeks of life. Even though exposure to many new organisms in the first days of life is undoubtedly great, a certain "inertia of infection" appears to exist However, after the first month colds are frequently characterized by coryza and a stuffy nose which interfere with nursing It is a common experience for a practicing pediatrician to receive a call from mothers when their babies are about six weeks of age stating that the baby seems to have its first cold and what should she do? There are no symptoms other than a stuffy nose and occasional sneezing This may be a critical illness for some babies and should not be passed off lightly as we know that many agents capable of producing the symptoms of a cold may progress rapidly, and serious complications such as meningitis or pneumonia may result Mothers who call regarding their babies' first colds may be advised to use nasal drops in order to facilitate nursing the baby. They should be alerted to the development of any other symptoms such as cough and dyspnea Postural drainage is frequently advised; placing the baby in a prone position on a firm mattress provides drainage of the upper respiratory areas and may prevent aspiration into the lower pulmonary passages In our state of ignorance we can probably safely advise the mother to keep the baby warm, away from drafts and unnecessary contact and travel outside the home

John H. Dingle in his presidential address before the American Association of Immunologists (April, 1958) discussed the "Curious Case of the Common Cold" He pointed out that although a tremendous number of papers representing extensive observations and investigations exist in the world literature, it is curious that the common cold remains so elusive and difficult to define. It is also curious that its epidemiology is so poorly understood and its causes are so uncertain. Dingle further states that a sharp definition of the

common cold is not possible and indicates that we should probably leave the definition to the patient who simply speaks of a "head cold" or a "chest cold."

ETIOLOGY AND EPIDEMIOLOGY

It is generally considered that the common cold is an infectious disease and probably due to certain viruses and perhaps even a single agent yet to be discovered. It is apparent that colds may be transmitted, albeit with some difficulty, from one individual to another by means of bacteria-free washings obtained from individuals suffering from acute colds. These observations date back to many investigators beginning with the classic studies of Kruse in 1914 and Foster in 1917. The infectivity rate of human volunteers is often less than 50 per cent of those subjected to challenge Elaborate human volunteer studies have been carried out in meticulous fashion by Andrewes and associates at the Common Cold Research Unit in the Harvard Hospital at Salisbury, England. Andrewes (1950) states: "It is probably true that the development of an overt cold in man is determined more by the varying susceptibility of the person than by the degree of exposure to the causal agent." He reports the successful cultivation of an agent of the common cold in tissue cultures of human embryonic lung. Filtrates from the tissue culture produced illnesses in 50 per cent of a group of human volunteers Passage, however, from one tissue culture to another reduced infectivity and after 10 passages only 10 per cent of the volunteers could be infected The agent failed to produce cytopathogenesis in tissue culture, and no means other than the inoculation of human volunteers has been found to indicate the presence of the virus

Over the years extensive studies of bacteria have been performed in order to find a cause for common colds Many have been considered responsible, such as the pneumococcus and

Hemophilus influenzae, which have been shown to increase and be present in great numbers in the presence of the common cold. There is no doubt that bacteria contribute to the continuing symptom picture and may be much more responsible for the manifestations of disease than the primary agent

The common cold is world-wide in its occurrence, although probably less ubiquitous in the milder tropical countries Isolated areas also appear to have a reduced incidence except when visited by outsiders. The Commission on Acute Respiratory Diseases has contributed a great deal of our epidemiologic information on the incidence of common respiratory diseases They state that from one to six episodes occur per year for any individual, varying of course with age and exposure In Cleveland families, Badger and his associates (1953) found an average of ten illnesses per year, six of which were classified as respiratory

Age has been recognized for many years as an important over-all factor in the prevention of colds, and it has been frequently stated that the only prevention for colds is getting older All investigators agree that the early years of life are correlated with the highest attack rate, which decreases during childhood to rather constant levels in adult life Reasons for differences because of age are not clear but have been thought to be due to immunity It seems possible that for many of the common respiratory illnesses immunity does play an important role with booster illnesses of a very mild or inapparent nature accounting for continuing immunity

Immunity to colds may not be absolutely related to the level of antibody, as human volunteer studies with the hemadsorption type 2 agent revealed that a cold-like illness could be produced in individuals who had measurable levels of antibody in their blood Some type of resistance to the *adenoviruses* is evident from the observation that second attacks failed to occur in persons found to be without specific

antibody at the time of exposure. Exposure undoubtedly plays an important role as a single child in the family during the preschool years has fewer colds than children in families with school-age siblings.

The Cleveland Family Studies incriminate the school-age child as the most frequent source of infection for the other members of the family. Gold and Robbins (1957) point out that the epidemic periods for colds correspond to the time when school is in session and indoor crowding is at its height. Increases in colds have been reported with changes in the weather, particularly changes correlated with severe cold. Paul and Freese (1933) also reported that epidemics of colds occurred aboard the icebreaker *Carnegie* upon entering cold ocean currents. Evidence to the contrary also is available in much of our literature. It is a fact that changes in temperature affect all people at about the same time, but colds do not follow this sudden epidemic pattern; rather they seem to radiate from a focal point at times of epidemics.

The experimental transmission studies of Andrewes, Lovelock, and Sommerville (1951) present the most convincing evidence with respect to environmental temperatures and their effect upon the host with respect to acquiring colds. They clearly showed differences with chilling and exposure so far as susceptibility of human volunteers was concerned. They demonstrated, however, that intimate contact is important and that direct contact in normal social exposure, such as playing cards with people suffering from colds or direct contamination of the air, was sufficient to bring on infection. One can conclude that intimate and direct contact is necessary in most instances for a legitimate exposure to be taken seriously. In their study, subjects with colds were found to be contagious as long as 24 to 36 hours before the appearance of symptoms, with contagiousness persisting for as long as seven days.

Little is known regarding duration of immunity, but it is

probably of brief duration as shown by Dochez (1933) in experimental colds in chimpanzees. In the classic studies of Paul and Freese (1933) in Spitzbergen, 75 per cent of the winter residents acquire respiratory disease within 30 days after the arrival of the first boat in the spring and 90 per cent experience at least one cold by the end of the shipping season. Multiple colds were also experienced by natives, and the interval of second attacks varied from three to seven weeks.

The Commission on Acute Respiratory Diseases (1947) demonstrated in human volunteer studies that severe common colds could be transmitted by individuals who had recently recovered, and 19 days following recovery a second challenge revealed the same susceptibility as existed initially The problem of immunity in the common cold is little understood, primarily because we know so little about the actual agents responsible for colds. Jackson, Dowling, and Anderson (1958) recorded studies on volunteers with infectious nasal secretions collected from persons with colds They employed four random matched groups of student nurses in each experiment and simultaneously administered one of two secretions Fifty-two per cent of individuals receiving nasal secretions in buffered salt solution developed colds The infectious secretions mixed with boiled human gamma globulin failed to alter the percentage of the volunteers who developed experimental colds When, however, the infectious secretions were incubated with human gamma globulin, colds occurred in only one-fifth as many subjects as in the groups just mentioned Statistically their studies were considered to be highly significant ($P = 0.001$)

In a study reported in 1946 by Adams and Smith, 70 medical students were studied throughout one respiratory season for the incidence of common respiratory disease. Gamma globulin was administered at monthly intervals to one-half of the group An initial dose of 6 ml of concentrated gamma

globulin was administered intramuscularly to each student in the experimental group. Thereafter, 4 ml of the same solution was given at monthly intervals; the subjects receiving a total of 30 ml in seven inoculations. The incidence of acute respiratory disease was reduced 40 per cent in experimental subjects as compared with the controls. The severity of illness was likewise significantly decreased in the experimental subjects as compared with their previous season's experience.

The study of Jackson, Dowling, and Anderson (1958) helps to confirm the possibility that for some colds at least there may be immunity and hope of active immunization.

COMPLICATIONS

The complications of the common cold are largely related to the development of secondary infection in cavities such as the middle ear and sinuses. The continuing purulent nasal discharge associated with colds, particularly in infants and children, may be caused by common bacteria such as pneumococci and usually responds to antibiotics Little evidence exists for the prevention of so-called secondary infection by the use of antibiotics. Although the common complications due to pneumococcus and streptococcus may be ameliorated, certain other types of organisms often take over and are responsible for complications. There is little reason to treat uncomplicated colds with specific drugs. When secondary infection occurs, antibiotics may produce very gratifying results *Indiscriminate use should be avoided because of the possibility of sensitization which is often unwarranted* The problem of antibiotics is discussed further in the following paragraphs under treatment and prevention.

TREATMENT AND PREVENTION

No specific therapeutic measures are available for the treatment of the primary symptoms of the common colds However, inasmuch as many of these infections become quickly

complicated or may occasionally be multiple, antibiotics should be employed when indicated. Diagnosis, therefore, becomes extremely important in such situations, and keen clinical judgment may be required. The use of aspirin in the proper dosage has been found to be helpful in many patients Flavored aspirin is not recommended for children because of the possible danger of poisoning. Dosage control is extremely important as salicylism may develop even from therapeutic doses in certain individuals. Nose drops designed to relieve congestion are sometimes helpful in nursing infants, and in children they may have some value in preventing middle ear infection Infants may need relief in order to nurse Humidity may be helpful, particularly in infants with symptoms of croup in association with acute respiratory illness No other drugs are recommended routinely except as the physician may determine indications Rest and warm clothing should be provided as well as avoidance of school and travel These measures not only have therapeutic but prophylactic value as they reduce exposure of other susceptible individuals

What is the evidence that tonsillectomy may prevent common recurrent respiratory disease? Studies which McCorkel and associates (1955) conducted on the occurrence of respiratory tract infection in Cleveland families are very helpful in this regard The illness rates in their two groups of children three years and older with and without tonsils showed no real differences The occurrence of respiratory infections before and after tonsillectomy revealed that between 5 and 10 years of age the attack rate of common respiratory disease during the year before tonsillectomy and the year after was similar when these rates were corrected for age and season. They cite the experience of children of the same age who did not have their tonsils removed and showed that by comparison the operation did not materially alter the average incidence of common respiratory disease.

Although the discovery of the *adenoviruses* failed to pro-

vide the hoped-for causal agents of common respiratory disease, many new and recent virus isolations appear to offer more hope that the etiology of the common cold is not completely obscure and may possibly be multiple.

Hope for control of colds is expressed by Ritchie (1958), who places a great deal of emphasis on the use of autogenous vaccines made from the individual's own nasopharyngeal flora. The cold rate per month for the controls was five times that of those who were vaccinated. Ritchie concludes that the patient's own pharyngeal flora bear a much larger share of his symptomatology than previously known. The use of autogenous vaccines markedly reduced colds; also short-term therapy by appropriate antibiotics reduced the incidence of colds

SUMMARY OF COMMON COLD

The common cold may be defined as a mild but acute respiratory tract infection primarily involving the mucous membranes of the nose and throat. This common infectious disease is thought to be caused by filterable agents, most likely viruses, that are transmitted by intimate contact between individuals. Very little immunity is produced by the agents of the common cold, and age appears to be the main factor in the decreasing incidence. The clinical signs of illness vary so tremendously from one patient to another and also in the same individual at different times that any sharp definition of the common cold is fraught with many risks. It is increasingly apparent that common acute respiratory disease may have numerous agents responsible for it. Many of our known viral agents may represent part of the answer as we are constantly reminded by those who know that a clear definition of the common cold is quite impossible The hypothesis of multiple etiology is appealing from many points of view It fits well into the recognized spectrum of illness due to many different etiologic agents bacterial and fungal as well as viral When

one considers the many immunologically distinct types of agents now known and discussed previously in this book it is not inconceivable that herein may lie part of the mystery of the common cold. The answer will probably come piecemeal Within the past few years these pieces have been coming in very rapid succession—so fast, in fact, that time does not permit an adequate evaluation of their relative importance in this complex field of common respiratory disease

ALLERGIC RHINITIS

Definition

Again we are faced with the difficult problem of definition A "cold in the head" is coryza, rhinitis, or a simple inflammation of mucous membrane, and the term, coryza, ordinarily designates acute rhinitis. The diagnosis of coryza or "head cold" is frequently made when the patient has acute congestion of the nasal mucous membranes. Rhinorrhea is a discharge of thin nasal mucus and is frequently referred to as a "cold." The diagnosis of allergic rhinitis may often be confused with infectious rhinitis As a consequence several factors are involved, such as allergic reactions of the nasal mucosa, viral infections primarily in the nose, bacterial infections, and psychosomatic disturbances If we were to select a virus as the cause of the common cold it would be a question of which one to select. Many known agents manifest themselves with symptoms and signs of a "cold" Emotional disturbances may lead to a flow of tears which may be associated with nasal edema and discharge. If no shedding occurs, then nasal obstruction frequently leads to a diagnosis of "common cold."

Allergic rhinitis includes both hay fever and perennial allergic disturbances which occur in certain seasons of the year during pollination These reactions are commonly asso-

ciated with the warmest months of the year. With perennial allergic rhinitis the causative allergen is not necessarily seasonal and may commonly be diagnosed as a "cold." The inhalant allergens are apt to be in dust (house dust or occupational dust), or animal danders including feathers and wool in garments and blankets. Face powder, molds, and other substances also may be included in the inhalant group. Ingestants, as a rule, are limited to foods and drugs. Allergy to bacteria has also been considered responsible for allergic rhinopathy.

Confusion therefore commonly occurs as a result of mixtures of factors that are impossible to separate. It is not inconceivable that allergy may produce a primary edema and congestion which in turn may be followed by infections of various sorts, which in turn may well respond to antibiotic or other specific therapy. Antiallergic therapy in such situations may also give relief.

Clinical Features

In the uncomplicated allergic rhinitis the mucous membranes are not usually as red as those involved in the acute and chronic conditions associated with infections Secondary infection, however, may occur along with the allergic condition at which time the allergic problem may be overlooked or missed Symptoms such as itching in the nose leading to coryza are considered characteristic of the sensory symptoms associated with allergic rhinitis. A chronic, irritative, unproductive cough may depend upon the same sensory disturbances in the larynx, trachea, or bronchi. A family history of allergic manifestations would be most helpful, but on the other hand the presence of allergic respiratory problems may be unknown and a diagnosis of sinusitis or chronic bronchitis dominates the history. The chronicity of the allergic problem is often prominent, and current or chronic periorbital edema

with mouth breathing may call attention for the first time to allergic nasal obstruction and congestion.

Mucopurulent discharges may clearly locate the child's difficulty in the nose or sinuses rather than in the tonsils or adenoids, but excesses of lymphoid tissue are very common in allergic children. Certain particular laboratory examinations are helpful in diagnosis but do not take the place of careful clinical observations. Eosinophilia in nasal secretions may indicate the allergic nature of the reaction. However, when infection is superimposed, a neutrophilic exudate usually predominates. Eosinophilia in the blood helps to confirm the clinical suspicion of allergy.

Skin tests are helpful in pointing to specific allergens but are only leads to the offenders which may actually be absent; negative tests do not exclude allergy. Clein (1954) points out that the occurrence of chronic rhinitis in infants may be related directly to allergy to cow's milk There may be associated gastrointestinal symptoms with nasal obstruction that frequently interferes with breathing and nursing. A therapeutic test of removal of the offending food (cow's milk) may bring prompt relief Allergic rhinitis in the first year of life is considered to be rare.

The sole manifestation of allergy may be recurrent, and chronic respiratory symptoms and many diagnoses are attached to these patients, such as allergic rhinitis, recurrent respiratory disease, sinusitis, vasomotor rhinitis, adenoids, colds, "a virus," etc Simple thickening of the mucous membranes occurs and may commonly be shown in the roentgenogram of sinuses Associated bronchitis with chronic cough leads to the syndrome often referred to as "sinobronchitis" Recurrent laryngeal symptoms have been considered as prominent manifestations of allergy, and allergic croup may resemble either spasmodic or the noninfectious croup which will as a rule respond to allergic management Such prob-

lems demand careful evaluation of the child and his environment from the allergic standpoint.

The most common aural manifestations of allergy are recurrent and chronic otitis media which, according to Vaughan (1957), result from the combination of infection in the respiratory passage and a basic allergic disorder. Brown (1954) expressed the opinion that adenoid hypertrophy has little or nothing to do with recurrent or chronic otitis media and believes that measures directed at control of the reactive changes in the nose and sinuses are indicated. In the presence of chronic disease in the nose and sinuses, a dual attack on allergy and infection may be strongly indicated. When possible, the examination of aural fluids may be most helpful in the diagnosis of an allergic condition as opposed to chronic infection. A predominance of eosinophilia in stained smears would strongly suggest an allergic condition.

Treatment

Diagnosis and management often go hand in hand as elimination of house dust, pollen, etc., may play a prominent role in the relief of the patient's symptoms and is often highly significant diagnostically. Except in early infancy, foods are considered of secondary importance but Vaughan (1957) suggests that certain highly allergic foods, such as chocolate, eggs, and nuts, may be easily excluded from the diet as well as those foods giving a positive skin reaction. The use of antibiotics when indicated may be combined with allergic management with good result. The first step should include antiallergic measures which may bring prompt relief of the patient's condition. Hyposensitization to the pollens or dust to which the patient has been shown to be sensitive should be carried out when the preceding measures fail to give relief. Seasonal hay fever may respond to a combination of hyposensitization and antihistamine therapy. In nonseasonal al-

lergic rhinitis, the offending allergens should be determined by history and skin testing and eliminated as far as possible, also hyposensitization by a series of injections should be carried out. Severe cases should seek relief by a change of climate.

REFERENCES

Adams, J M, and Smith, N (1946) · Clinical trial of gamma globulin in the prevention of common respiratory diseases, *Proc. Soc Exper. Biol & Med*, **63** 446

Andrewes, C. H (1950). Adventures among Viruses. III Puzzle of common cold, *New England J Med*, **242** 235.

Andrewes, C. H (1951): The common cold, *Scient. Am.*, **184** 39

Andrewes, C. H (1953) · Propagation of common cold virus in tissue culture, *Lancet*, **2** 546

Andrewes, C H; Lovelock, J E, and Sommerville, T (1951). Experiment on transmission of colds, *Lancet*, **1**·25

Badger, G F., and others (1953) A study of illnesses in a group of Cleveland families II Incidence of the common respiratory diseases, *Am. J. Hyg*, **58**.31

Brown, E E (1950) Fifty symptoms of chronic sinusitis in children, *Arch Pediat*, **67** 503

Brown, E. E (1954) Harmful sequelae of adenoidectomy in children, *Arch Pediat*, **71** 233

Bryan, W T K, and Bryan, M P (1953) Structural changes in the ciliated epithelial cells during the common cold, *Tr Am Acad Ophth*, **57** 297

Chanock, R. M, Parrott, R H, Cook, K, Andrews, B E, Bell, J A, Reichelderfer, T, Kapikian, A Z, Mastrota, F M, and Huebner, R J (1958) Newly recognized myxoviruses from children with respiratory disease, *New England J Med*, **258** 207

Clein, N W (1954) Cow's milk allergy in infants, *Pediat Clin North America*, **1** 949

Commission on Acute Respiratory Diseases (1946) A study of the effect of oiled floors and bedding on the incidence of respiratory disease in new recruits, *Am J Hyg*, **43** 120

[illegible] Acute Respiratory Disease [illegible] J. Clin. [illegible]

[illegible] Rowe [illegible] 1965 [illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

[illegible]

Jackson, G. G; Dowling, H F.; and Anderson, T. O. (1958): Neutralization of common cold agents in volunteers by pooled human globulin, *Science*, **128**:27.
Jordan, W. S, Jr., and Dingle, J. H. (1954): Acute upper respiratory infections, *GP*, **10**:49.
Kern, R. A (1947): Perennial allergic rhinitis: The most important respiratory allergy, *M. Clin. North America*, p 1375
Kruse, W. (1914): Die Erreger von Husten und Schupfen, *Munchen, med Wchnschr.*, **61**:1547 Quoted by Greenspan, F. (1943): *Arch. Pediat*, **60**:90.
Lovelock, J. E.; Roden, A T.; Porterfield, J S, Sommerville, T; and Andrewes, C H (1952): Further studies on the natural transmission of the common cold, *Lancet*, **2** 657
McCorkle, L. P.; Hodges, R G; Badger, G F, Dingle, J H, and Jordan, W. S, Jr (1955) A study of illness in a group of Cleveland families. VIII Relation of tonsillectomy to incidence of common respiratory diseases in children, *New England J. Med.*, **252** 1066
Paul, J. R, and Freese, H L (1933) Epidemiological and bacteriological study of "colds" on an isolated island (St John, Virgin Islands), *J Exper Med*, **53** 733
Ritchie, J. M (1958) Antibiotics in small doses for the common cold, *Lancet*, **1** 618
Ritchie, J. M (1958) Autogenous vaccine in prophylaxis of the common cold, *Lancet*, **1** 615
Vaughan, V. C (1957) Allergic problems in the upper respiratory tract, including the ear. Respiratory Disorders, *Pediat. Clin. North America* (Feb) p 285

APPENDIXES

(13) Differentiate in blue differentiator 3.5 min
  (a) phosphotungstic acid 25 gm
  (b) picric acid 2.5 gm
  (c) 95% ethyl alcohol 100 ml
  (d) distilled water 400 ml
  (until fuchsin-colored cells are clear of blue and hyalin and collagen are clear blue)
(14) Wash quickly in distilled water
(15) 2% acetic acid in water 1 min
(16) 2% alcoholic acetic acid ½ min
(17) Absolute alcohol ½ min–3 min
(18) Xylol 5 min
(19) Cover slip

HEMATOXYLIN AND EOSIN STAINING PROCEDURE

Fixation: 10% neutral formalin
  Run sections down to water
(1) Stain in Delafield's hematoxylin (diluted 1:5) 4 min
(2) Rinse in tap water
(3) Differentiate in 1% hydrochloric acid until nuclear structures are clear and cytoplasm is light gray
(4) Stop acid action by dipping into 1% ammonium hydroxide
(5) Running tap water 10 min
(6) 50% ethyl alcohol 3 min
(7) 70% ethyl alcohol 3 min
(8) 95% ethyl alcohol 3 min
(9) Counterstain with 1% alcoholic solution of eosin 30 sec
(10) 95% ethyl alcohol, 2 changes to remove excess stain
(11) 100% ethyl alcohol 3 min
(12) Xylol—100% ethyl alcohol (1:1) 3 min
(13) Xylol 5 min

HEMATOXYLIN-SHORR STAINING PROCEDURE

Preparation of Shorr stain

(1)	Ethyl alcohol, 50%	100 ml
(2)	Biebrich scarlet (water soluble)	0 5 gm
(3)	Orange G	0 25 gm
(4)	Fast green FCF	0 075 gm
(5)	Phosphotungstic acid, cp	0 5 gm
(6)	Phosphomolybdic acid, cp	0 5 gm
(7)	Glacial acetic acid	1 0 ml

Procedure.

(1)	Fix smear or impression while still wet in equal parts, ether and 95% ethyl alcohol	1–2 min
(2)	70% ethyl alcohol	3 min
(3)	Distilled water	3 min
(4)	Hematoxylin (Delafield's, diluted 1.5) Differentiate in 1% hydrochloric acid and stop acid action in 1% ammonium hydroxide solution	4 min
(5)	Running tap water	10 min
(6)	Shorr stain	2 min
(7)	70% ethyl alcohol; few dips to remove excess stain	
(8)	95%, 100% ethyl alcohol	3 min each
(9)	Xylol	5 min
(10)	Cover slip	

In a properly prepared slide, the nucleus will be bluish purple, the cytoplasm pale green, and the inclusion bodies bright red

MACHIAVELLO'S STAINING PROCEDURE

Prepare the following stock solution

Basic fuchsin	0.25 gm in 100 ml double distilled water
Citric acid	1 gm in 200 ml double distilled water
Methylene blue	1 gm in 100 ml double distilled water

After air drying smear or impression preparation, fix by heat

(1) Basic fuchsin (pass through filter paper in funnel) 5 min
    (a) Drain off stain
(2) Citric acid solution; dip for a few seconds
(3) Wash thoroughly with tap water
(4) Methylene blue solution 20–30 sec
(5) Wash with tap water
(6) Air dry

In a properly prepared slide, most of the elementary bodies will be stained bright red, other elements stain blue.

Appendix B

COMPENDIUM OF TREATMENT, DOSAGES

VIRAL PNEUMONIAS

Psittacosis	Tetracycline, 4 gm daily—2 days, *then* 2 gm daily until recovery, *or* 50 mg per kilogram—initially, *then* 50 mg per kilogram daily in divided doses
Influenza, variola, varicella, rubella, lymphocytic choriomeningitis, *adenovirus* pneumonia, infectious mononucleosis	No specific treatment for primary illness, but chemotherapy for secondary infections as indicated
Erythema exudativum multiforme	Steroid therapy may be helpful
Primary atypical pneumonia	Tetracycline, 0 5 gm every 6 hr, or 40–50 mg kilogram/day, or treat secondary infection as indicated

RICKETTSIAL PNEUMONIAS

Fever	Tetracycline or chloramphenicol, same therapy as outlined for psittacosis

MYCOTIC INFECTIONS

Actinomycosis:	Penicillin, 1,000,000–2,000,000 units daily, or tetracycline as suggested for psittacosis
Nocardiosis:	Sulfadiazine, 4 gm daily, or tetracycline as suggested for psittacosis
Histoplasmosis:	Amphotericin B, 0.5–1 mg per kilogram daily, intravenously in slow 6-hr drip—30–60 days depending on reaction
Coccidioidomycosis:	Amphotericin B (same as for histoplasmosis)
Moniliasis:	Amphotericin B (same as for histoplasmosis), or Mycostatin for intestinal infection
Cryptococcosis, aspergillosis, geotrichosis or penicilliosis	Amphotericin B (should be tried as recommended above for histoplasmosis)
Blastomycosis and sporotrichosis:	Potassium iodide or 2-hydroxystilbamidine 250 mg daily in 250 or 500 cc of 5% dextrose intravenously in slow drip, 30–60 days, amphotericin B as outlined above for histoplasmosis

Appendix C

THE REOVIRUSES

Recently Sabin (1959) reported a new group of viruses, the *reoviruses*, formerly classified as ECHO, type 10. They are larger than the *enteroviruses*, measuring approximately 72 mμ, and are clearly associated with respiratory and enteric illness in human beings, chimpanzees, and monkeys The *reoviruses* produce lesions in the brain, liver, and myocardium of newborn mice, and Sabin suggests that they must be considered as a potential cause of disease in the newly born

Three types have been delineated, the prototype or "Lang" strain is type 1, formerly ECHO, type 10 All of the strains have a common complement-fixing antigen, but possess distinct differences antigenically in neutralization and hemagglutination-inhibition tests

The original strains were first isolated from healthy children in Cincinnati, and subsequently from chimpanzees with spontaneous rhinitis, from a family with enteritis, and from children with diarrhea The *reoviruses* must be included in any systematic study of the complex viral etiology of respiratory and enteric diseases

REFERENCE

Sabin, A. B (1959). Reoviruses, *Science*, **130**·1387.

Index *

* Numbers in **boldface type** indicate primary discussion of the topic